ANNALS
OF THE
RHEUMATIC DISEASES

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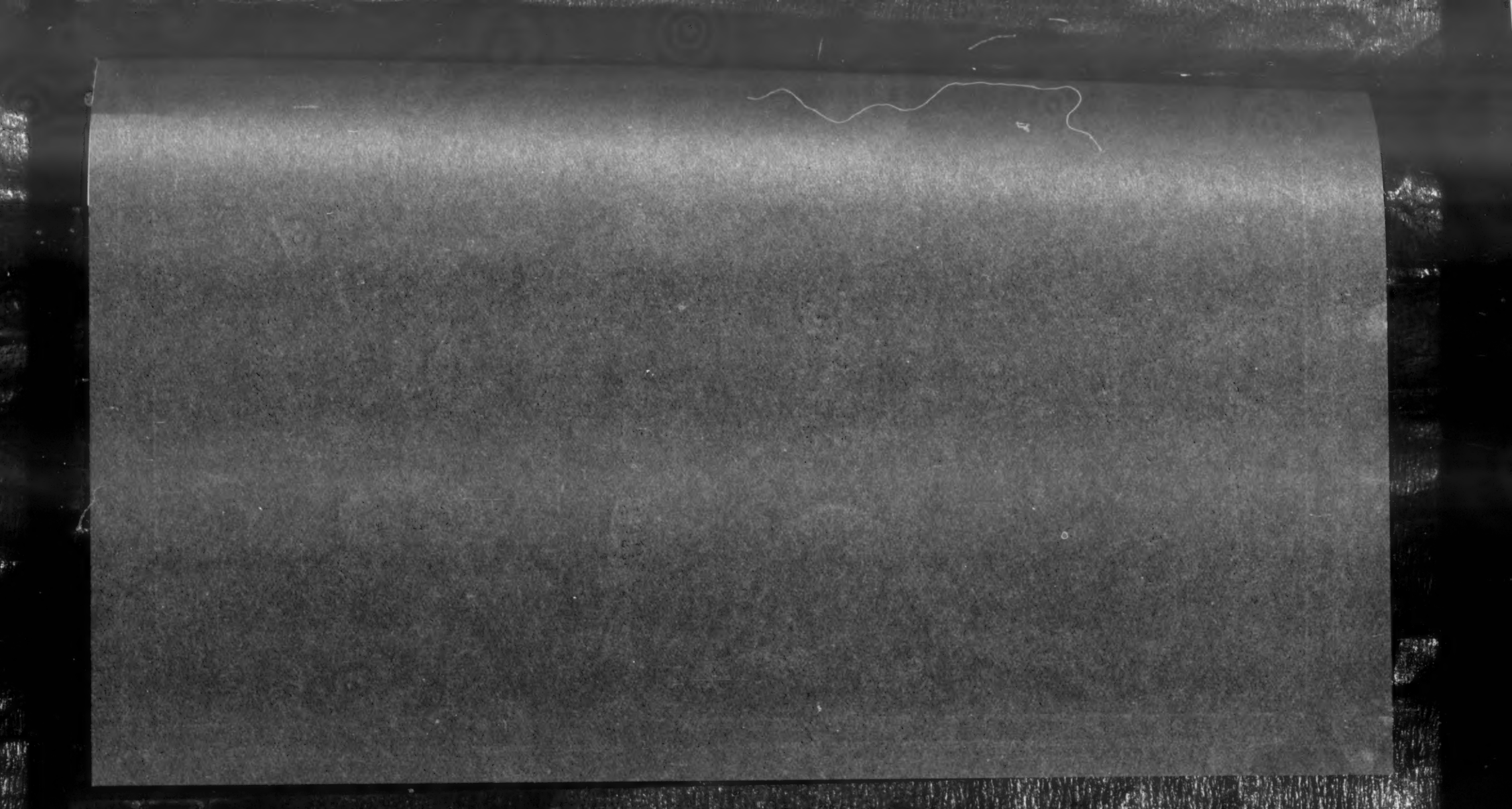

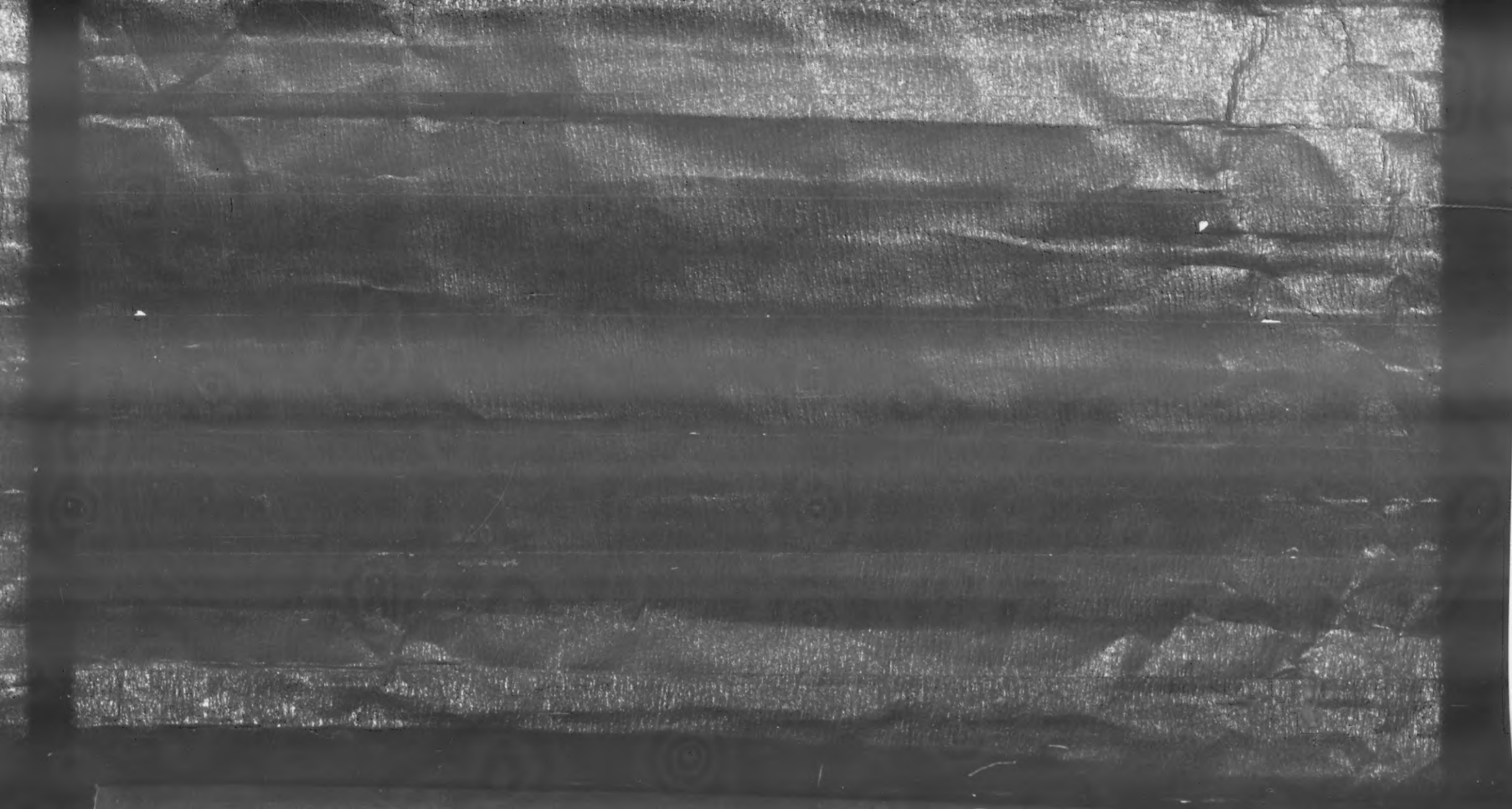

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THE OFFICIAL JOURNAL OF

THE EMPIRE RHEUMATISM COUNCIL

Owing to war conditions and the need for economy in paper, two issues only of "Annals of the Rheumatic Diseases" will be published this year, instead of four. Subscribers' payments will be adjusted accordingly.

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ANNALS
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THE WAR ON RHEUMATISM

By LORD HORDER
Chairman, Empire Rheumatism Council

The conclusion of five years of work and the opening of a new volume of our official journal prompt a brief survey of our achievement and our future prospects.

At the outset let me record the following letter from H.R.H. the Duke of Gloucester, for whose continued warm interest we are heartily grateful:

> "As President, I congratulate you and your colleagues on the very good progress made by the Empire Rheumatism Council during 1941.
>
> "It is particularly encouraging to note that, thanks to prompt action in sending out missions of enquiry to the Rheumatism Treatment Centres of America and Europe before the outbreak of war, you are now able to present a plan of treatment based on international as well as British practice.
>
> "I warmly welcome the close connection with the American Rheumatism Association. In this field of humane effort, as in so many others, the best hope for the world rests with the friendly co-operation of the English-speaking peoples."

Since readers of the Annals have had the opportunity of studying our Annual Reports (the fifth was published in the last number), a mere factual record would be redundant. I prefer to take this occasion to examine the case of the Opposition —for there *is* an Opposition, few in numbers and, I believe, mistaken in outlook—as a convenient means of measuring our achievement.

One critic of our Fifth Annual Report complains that, after five years' work, we have not yet discovered the primal cause

of rheumatism. That shows a strange misunderstanding of the nature of the task of the research worker in this field. It is clear enough to the instructed mind that we are dealing with a congeries of disease processes, and not with a single disease. A primal cause is therefore not our aim. Our aim is the discovery of new facts which, together with those already known, will enable us to piece together the jig-saw puzzle which we call "Rheumatism." But in convincing a community (as we must strive to do) of the necessity of our task, and that it is being diligently pursued, we are not dealing solely with instructed minds. It is wise, therefore, to take every opportunity to explain the high degree of patience and labour demanded by medical research in its quest for the elusive causative agencies of disease and to emphasise the many trails which must be followed because they give promise at first but, followed to their end, lead nowhere, or do not lead to the particular end in view. It is sufficient to justify a research campaign, covering so wide a field as ours, if it can show that it has been industrious and intelligent in using its resources. We may claim that credit. Altogether we have financed, or have assisted in financing, sixteen distinct research efforts extending over long periods. All of them have given some hint as to the solution of the problems confronting us. In some cases the hint has been positive, suggesting that we are on the right track. In other cases it has been negative. Both classes of hint have value. All criminal investigators, whether the professionals or those brilliant amateurs familiar to readers of "thrillers," agree that a useful part of their task is by inquiry to exclude from a group of suspects those who are evidently not guilty.

The most extensive of our research efforts so far has been that into the causes of the incidence of acute rheumatism in the training establishments of the Royal Navy. This inquiry gives good promise of some definite results. If so, the credit will belong equally to the E.R.C. and the Admiralty Medical Services, since the latter made this investigation possible and gave it cordial help. The research is being continued in spite of the war.

Unhappily, serious handicaps on our research work have been inflicted in other directions by war conditions. The intention to bring to Great Britain one of a group of Polish scientists, who had very substantial evidence to support their claim to have

discovered a serological test of value in rheumatic disease (a most important achievement if the claim is substantiated), was frustrated by the outbreak of the *furor teutonicus*. Pertinacious effort through several diplomatic agencies to discover if these Warsaw workers are still alive has failed. Also, one of our Travelling Fellows barely escaped from Central Europe in 1939. Those are but two out of several war incidents which have affected our work. Yet it would not be right to give the impression that, but for the war, a five years' term would have been sufficient. Scientifically we can state no exact term. All we can say is that there is ground for believing that it will be a reasonably short term and that, humanly speaking, success is certain.

Already we have made considerable progress in that section of our work which deals with the means of treatment of rheumatic disease. Last year we felt justified, after a prolonged and systematic investigation of all the problems involved, in placing before the profession and the lay interests concerned the " blue print " of a plan by which a community could put to practical use the means by which, in the present state of medical knowledge, the crippling ravages of rheumatic disease can be greatly limited. The plan was admittedly tentative: it was intended as a basis for discussion, to bring the issue into the region of practical medical politics. The medical and the lay Press were specifically invited to criticise the proposals made in this scheme. There has been a remarkable absence of any adverse criticism, though much highly favourable comment. No one has said that the plan is unnecessary or impracticable. There have not been even suggestions for amendment in detail, though these we must expect (and shall welcome) as progress goes from the " blue print " stage to that of installing the machine tools and designing the lay-out. Without bringing into the balance those considerations of humanity which urge us to action against what, in the mass, is the greatest cause of pain in modern life, it may be said that this matter of treatment has been narrowed down to the question, " Shall we grudge a penny and waste a pound ?" Perhaps some of us, looking out upon the world of today, may question the advantage of that longer life which medical science, with the assistance of its lay helpers, is giving to man. None will question the advantage of a more pain-free life.

Finally, but by no means least importantly, the Empire Rheumatism Council can congratulate itself on the fact that,

within the term of five years, it has secured a close Anglo-American alliance in the War on Rheumatism. That, as our President notes, is of supreme value. There is no humane scientific task beyond the range of our joint accomplishment; and we shall be reinforced in due course by the efforts of Russia, of China, and of the liberated peoples of Europe.

HÆMOLYTIC STREPTOCOCCAL INFECTIONS AND ACUTE RHEUMATISM*

By C. A. GREEN

NOTE.—This paper summarises the contents of a thesis presented for the M.D. degree to Edinburgh University. The thesis served the dual purpose of reporting in detail the work carried out during three years' tenure of the Sir Halley Stewart–Frederick Pearson Research Fellowship of the Empire Rheumatism Council, and of indicating the interrelationship of the various problems which have been studied.

General Introduction

RHEUMATISM now rivals tuberculosis as the infective disease which most seriously impairs the economic efficiency of Great Britain. The extent of the problem may be gathered from such facts as that the London County Council alone expends almost £250,000 annually on the prevention and treatment of juvenile rheumatism. Whereas vigorous counter-measures have produced a steady decline in the incidence of tuberculosis, it is unlikely that a parallel reduction in rheumatism has occurred. It is a regrettable omission in public health administration that acute rheumatic fever is rarely notifiable. The approximate incidence can only be deduced from returns issued by sections of the community. These indicate that the severity of the disease, particularly in regard to the appearance of cardiac complications, has increased in certain sections of the community from whom statistical returns are available.

Surveying the end results in a series of 300 cases of juvenile rheumatism, Wallace (1937) recorded that 25 per cent. of all rheumatic children died from heart disease before they reached school-leaving age, and a further 30 per cent. were crippled for life. This did not appear to be a local excess, for in the London area 20 per cent. of rheumatic children were fit only for light employment when they left school. Davidson and Duthie

* Received for publication March 7, 1942.

(1938) have shown that, of the total population of 5,000,000 in Scotland, 50,000 insured persons were wholly incapacitated each year for an average of sixty days. They estimate that there must be approximately 335,000 new cases of rheumatism each year in Scotland, of which 26,000 were cases of acute or subacute rheumatic fever. This condition produces its maximum effect in childhood and adolescence. Thus Hedley (1940) has recorded that 63 per cent. of cases admitted to hospitals in Philadelphia from 1930 to 1934 were under fourteen years. If these facts were capable of general application then it may be deduced that in Scotland alone there are approximately 3,000 deaths per annum in children as a result of acute rheumatism, and the same number leave school as cardiac cripples. Should acute rheumatism finally prove to be yet another manifestation of hæmolytic streptococcal infection, then the group of diseases due to this organism will undoubtedly constitute the greatest of all future problems in preventive medicine.

Part I.—Epidemic Scarlatina

Although the great advance in the treatment and prophylaxis of hæmolytic streptococcal infections which followed the introduction of the sulphanilamide group by Domagk (1935) was probably the most outstanding achievement in the experimental field, less spectacular but equally important studies have been made in other directions. Thus the serological work of Griffith made possible extensive epidemiological studies which were previously impracticable. Griffith (1934) noted the predominance of types 1, 2, 3 and 4 of *Streptococcus pyogenes* in scarlatina, a distribution confirmed by Neisser (1939) for strains isolated in the London area and by Kodama *et al.* (1939) for strains isolated in Tokyo. Part 1 of this thesis (Green, 1937) showed that this distribution did not apply to the 1933 epidemic of acute scarlatina in Edinburgh in which eight serological types were recognised. Of the 1,581 cases examined, 47·8 per cent. were due to type 5 cases, whereas Griffith's types 1, 2, 3 and 4 constituted 29·3 per cent. of the total. In March, two months before the onset of the epidemic, there was already a marked preponderance of type 5 cases in those admitted to hospital. During that month type 5 cases comprised 43·24 per cent. of the total, the next largest group being type 3, with 22·97 per cent. During April the proportion of type 5 cases remained approximately the same.

In May with the rise of the epidemic the proportion of type 5 cases mounted to 58·3 per cent., and in June had reached 78·5 per cent. From this peak period the proportion of type 5 cases fell during the next three months to 42·3 per cent., but in the same three months the absolute number of type 5 cases remained approximately the same. This fall in the proportion of type 5 cases was largely compensated for by a rise in the number of type 3 strains. The outbreak was therefore associated with an overwhelming predominance of a single type, but was maintained by a succession of rises in the incidence of all the types present at the outset rather than a continued multiplication of the original dominant type. No evidence was obtained regarding the particular function or property of the organism upon which this rise in the case incidence depended. An investigation of the toxin production of strains isolated at different periods of the epidemic (Green, 1935) showed that there was no significant variation among the strains studied. Hæmolytic streptococci were isolated from the throat in 36·8 per cent. of patients on discharge from hospital, but in only 5·4 per cent. was a large number of organisms detected. In the majority of cases the type isolated on discharge was the same as the admission strain. This would appear to indicate that the scarlatinal strains exhibit serological stability to a considerable degree. In a certain number of discharged patients an additional strain was recovered which failed to agglutinate with specific sera against any type. Continued growth of the original infecting strains in the secretions of persons undergoing active immunisation against those strains was thought to be a possible explanation for this inagglutinable type of organism. An attempt to restore the original type characteristics by raising the virulence by animal passage was unsuccessful. This observation has since been confirmed by Neisser (1939), who reported that strains from convalescents tended to be less easily agglutinated and frequently seemed to have lost the type-specific agglutinogens. There was a tendency for type 5 and type 3 strains to be found with relative frequency in the discharge examination of convalescent cases from whom some other type had been isolated in the acute stage. This may have been due to an increased capacity of these particular strains to spread from patient to patient, but a more likely explanation is to be found in the fact that these strains were in much greater concentration in the wards from the acute stage onwards.

Reviewing the age groups in which cases occurred, there was a remarkable lack of differentiation as between the non-epidemic years 1931, 1932 and 1934 and the epidemic year 1933. A low incidence at all ages up to five years was followed by a very sharp rise in the curve till the peak was reached between five and ten. Thereafter the decline in incidence with increase in age was rapid but regular, there being a small rise between twenty and twenty-five due to cases in young mothers of children returning from hospital. During those years there was a very marked difference in the actual number of cases, there being a total of 564 in 1931 and 3,461 in 1933—a sixfold increase. During the epidemic year of 1933, all age groups were equally affected by the outbreak since the increase in the number of cases was proportionate in all age groups, the characteristic maximum age-group incidence between the ages of five and nine years being maintained. As far as the exposed population was concerned, there appeared to be two possible explanations for this proportionate increase in case incidence. Firstly, the causal factors of the epidemic were universally at work in all age groups, or, alternatively, an increase in the cases at some particular age group was attended by a secondary rise in all other age groups. The increase was simultaneous, pointing to the existence of some universal contributory factor. The results obtained point to the general conclusion that the origin of this epidemic was associated with some still undiscovered property of the infecting organism rather than with any exceptional variation in the affected community.

At the suggestion of the author, the investigations were continued in Edinburgh by de Waal (1940, 1941). In a less extensive outbreak of scarlatina in the autumn of 1937, the majority of cases were found to be due to type 1, while type 4 was predominant in a mild epidemic of scarlatina in 1938. The complete absence of type 5 cases in those two years was in marked contrast to the incidence in the heavy epidemic of 1933, although the wave-like action of various types in maintaining the epidemic was noted. The effect of such waves must be the production of a state of flux in the general immunity of the population, for the predominance of certain types is not confined to clinical cases but extends to healthy subjects in the area, as shown by Kodama (1939). An instance of the probable sequence was afforded by the observation of Keogh (1939) that an epidemic

of type 2 infection in a ward of 59 children produced 16 cases of scarlatina, while 23 contracted type 2 infection without rash. Evidence was obtained that a number of children who failed to develop a rash owed their resistance to a previous type 6 infection which did not produce rashes.

Part II.—Hæmolytic Streptococci in Acute Rheumatic and Control Groups

Clinical data regarding the frequency with which tonsillitis occurred in rheumatic subjects were supplied by the work of St. Lawrence (1920), Ingerman and Wilson (1924), Poynton (1925), Bertram (1925), and McCulloch and Irvine-Jones (1929). In these investigations the incidence of throat infections was found to vary from 22·4 per cent. to 77 per cent. Additional proof of the prevalence of repeated infection was found in the condition of the fauces. Thus the St. Thomas's Hospital data in the Medical Research Council 1927 report on rheumatism showed that the proportion of healthy throats in children of non-rheumatic families was greater than that in rheumatic families. In a similar controlled investigation Lambert (1920) found that in 1,000 consecutive cases of rheumatism the proportion of unhealthy throats was 25·3 per cent., as compared with 16 per cent. in 250 cases of acute pneumonia. Active infection as indicated by inflammation of the throat was present in 22·4 per cent. and 0 per cent. of rheumatic and control groups respectively. Perhaps a more striking demonstration of the connexion between the two conditions is supplied by the occurrence of outbreaks of rheumatism, mainly of recurrent attacks but sometimes primary, after epidemic tonsillitis. Many examples of this sequence are described in the literature by Raven (1923), Boas and Schwartz (1926), Hiller and Graef (1927-8), Glover (1930), Schlesinger (1930), Glover and Griffith (1931), Collis (1931), Sheldon (1931), Bradley (1932), and Coburn and Pauli (1935*b*).

While there is thus considerable evidence for the occurrence of tonsillitis in rheumatism, the bacteriological examination of the throat flora in such cases has yielded divergent results. Although the streptococcal genus has attracted most attention, many species within the genus have been incriminated by different observers. Within recent years, beta hæmolytic strains have gained increasing recognition in the reports of Glover (1930), Coburn (1931), Glover and Griffith (1931), Collis (1931), and

Bradley (1932). Similar investigations, such as that described by Schlesinger (1930), have led to the view that no single type of organism could be recognised as responsible for all infections, but that many species were involved. It may be noted that, in the majority of investigations in which beta hæmolytic streptococci have appeared important, the type of nasopharyngeal infection has been of the epidemic variety in enclosed populations such as those of schools, hospitals and training quarters. It is commonly recognised that hæmolytic streptococci from human sources differ greatly in pathogenicity as determined by virulence tests in experimental animals; but the method is not suitable for extensive investigations, nor does the pathogenicity in man and animals always concur. Lancefield (1933), by means of a precipitin test, claimed that hæmolytic streptococci could be divided into groups, each of which possessed a common group-specific carbohydrate fraction (M). Furthermore, group A represented the important pathogens in the human nasopharynx, but not all commensal strains in this site belonged to group A. Hare (1935), for instance, examining the nose and throat of normal human beings, noted that only about one-third of hæmolytic streptococci isolated were group A, the carrier rate of this type in a normal population being estimated to be approximately 7 per cent. The relatively low proportion of commensal group A strains in normal persons has been confirmed by Davis and Guzdar (1936), who recorded a carrier rate of 3 per cent. Again, Plummer (1935) classified all but two of 418 strains from human infection in group A, but found that many strains from healthy subjects were not of this group. However, a much higher proportion of carriers has been recorded by Kodama (1937), who found that 68 per cent. of fifty normal subjects were in this category.

Clearly this method of examination was applicable in an investigation (Green, 1938*a*) into the part played by hæmolytic streptococcal infection of the nasopharynx in rheumatic subjects. Two groups of subjects were examined, each numbering 200 and constituted as follows:

Group R.—Patients admitted to hospital with one or more symptoms of acute rheumatism, including arthritis, carditis, chorea, etc. This group included subjects with both initial and recurring attacks which were of sporadic distribution.

Group NR.—Patients in the same hospital wards as members of group R, but without existing or previous manifestations of

rheumatism. This group included all types of diseases and no discrimination was made as to the presence or absence of naso-pharyngeal infection. In 156, or 78 per cent., of the rheumatic group R a history of infection within the preceding six weeks was obtained. On admission to hospital with rheumatic manifestations the throat symptoms had entirely subsided in the majority of cases, although enlarged tonsils were often found. Turning to the control group NR, a high figure of recent infection was also found—namely, in 93, or 46 per cent.

From the throat swabs taken on admission from group R, hæmolytic streptococci were isolated in 116, or 58 per cent. of patients. In the case of the control group NR, 59, or 30 per cent., were found to be carriers. Considering the results in respect of recent throat infection, 59, or 60 per cent., of the 156 rheumatic patients with a positive history gave positive cultures of hæmolytic streptococci, whereas 21, or 47 per cent., of the remaining 44 with a negative history yielded positive cultures. In the control group NR the hæmolytic streptococcal carrier rates in those patients with and without known recent infection were 28 and 30 per cent. respectively.

The most important of the data secured by the application of the precipitin test was the high proportion of group A strains isolated from group R patients as compared with group NR. Whereas the difference in incidence of hæmolytic streptococci —namely, 58 per cent. and 30 per cent. respectively—in these two groups was notable, the difference in the incidence of group A infection was even more significant, the respective incidences being 50·5 and 12·5 per cent. Further, it was found that although the majority of persons in the control group with a history of recent infection were group A carriers, only 7 of 33 persons without recent symptoms were carriers. On the other hand, rheumatic subjects irrespective of subjective symptoms of infection yielded group A strains in the majority of instances where hæmolytic streptococci were isolated.

The number of subjects in each of the two groups examined was large enough to enable reasonable comparison to be made. A high incidence of sore throats in the rheumatic group—namely, 78 per cent.—was not unique, but approximated to that found by St. Lawrence (1920) and Ingerman and Wilson (1924). In an unselected control group it was surprising to find the incidence of recent sore throats to be as high as 46 per cent., but for purposes

of comparison in regard to the bacteriological investigations this was a fortunate occurrence. As hæmolytic streptococci were recovered from 58 per cent. of all rheumatic subjects on admission to hospital, an indication was obtained of the extent to which this type of organism was responsible for the preceding throat infection noted in many of the series examined. It is recognised that faucial infections with this organism, as in scarlet fever, are followed by the carrier condition for indefinite periods, and it was reasonable to assume the same sequence in the present investigation. Of rheumatic patients with subjective symptoms of preceding infection, 60 per cent. yielded hæmolytic streptococci, whereas in the symptomless the carrier rate of 44 per cent. was still high. On the other hand, in the control group, despite the prevalence of apparent recent infection, only 30 per cent. yielded hæmolytic streptococci, and approximately the same proportion of carriers was found in those with and without recent history. This would suggest either that in the control group many of the throat infections were due to organisms other than hæmolytic streptococci, or that the carrier condition after faucial infection was less persistent than in rheumatic subjects.

Part III.—Sensitivity of Rheumatic Subjects to Streptococcal Products

It is commonly recognised that the percentage of Dick-positive reactors among rheumatic subjects differs little from that in the general population. The condition does not appear to be related to lack of antibody to the erythrogenic toxin, but does not exclude the possibility that other exotoxins play some part, although they remain unrecognised.

On the other hand, there has accumulated considerable evidence to suggest that part of the rheumatic syndrome may be an expression of the allergic or hypersensitive state. The work of Swift, Derick and Hitchcock (1928) led to the conclusion that the hypersensitivity of the individual was more important than the specificity of the infecting organism. In this way the divergent findings of investigators as to the causative organism could be reconciled. Birkhaug (1929) found that a common allergenic factor was present to a relatively great extent in *viridans* and indifferent streptococci, and to a less extent in hæmolytic streptococci. Irvine-Jones (1928) also reported on the non-specific nature of the allergic reaction to streptococcus

extracts. Coburn (1931) has been able, however, to utilise this method in associating rheumatism particularly with naso-pharyngeal infection due to hæmolytic streptococci. Collis (1931) has corroborated this work, but Gibson, Thomson and Stewart (1933) concluded that, although positive reactors to hæmolytic streptococcal endotoxin were more common in rheumatic than in control cases, skin sensitivity could not be regarded as an indication of a special reactivity necessary for the production of acute rheumatic infection. On the assumption that hypersensitivity was an important factor in the production of the rheumatic state, treatment by desensitisation has been attempted. Collis and Sheldon (1932) employed intravenous vaccination with hæmolytic streptococci with moderately successful results. Treatment had to be stopped in the presence of focal infection of the throat with hæmolytic streptococci.

Many of the patients examined in the previous investigation were tested for hypersensitivity to various streptococcal products (Green, 1938*b*). At the outset an attempt was made to test with preparations from autogenous strains of streptococci isolated from throat swabs of acute cases of rheumatism on admission to hospital. Only those subjects were selected from whom hæmolytic, *viridans* and indifferent streptococci were all isolated. The preparations were the purified Dick toxin and endotoxins of the hæmolytic (H.S.E.), *viridans* (V.S.E.) and indifferent (I.S.E.) streptococci. In all, 32 cases of acute rheumatism were tested within ten days of admission to hospital. Of the 32 cases, 7 gave positive reactions to Dick toxin. On the other hand, 27 patients reacted positively to H.S.E. Although 14 persons reacted to V.S.E., 11 of these were also sensitive to H.S.E. and only 3 reacted to V.S.E. alone. Similarly 11 of the 13 subjects reacting to I.S.E. also reacted to H.S.E. Further, in those patients who reacted to all three endotoxin fractions, the reaction to H.S.E. was almost invariably the greatest.

While the susceptibility to erythrogenic exotoxin was no more than was expected in an average population, and agreed with the accepted findings in regard to Dick reactions in rheumatism, the frequency of reactions to H.S.E. indicated that particular attention should be paid to this in an extended series of cases. The use of autogenous products had proved exceedingly laborious and was impracticable for a large group. Accordingly, standardised mixtures were prepared and used for intradermal tests on two

large groups of patients, as described in the previous investigation. In group R were included all cases with acute and subacute rheumatism, while group NR was composed of non-rheumatic patients and included all types of diseases. There was again no significant difference in the percentage of positive reactors to exotoxin in the two groups—namely, 24·8 and 29·4. The response to endotoxin revealed a definite difference between the two groups as a positive reaction was present in 71·4 per cent. of group R as compared with 23·3 per cent. in group NR. Further, the percentage of positives in patients in the acute stage of illness was higher than in the subacute phase, except in the small group of choreics, where only half were positive.

In view of these findings it appeared to be rational to attempt to desensitise rheumatic patients. Serial subcutaneous injections of H.S.E. were given and in the majority of cases provoked no response other than slight local discomfort. In a few individuals certain suggestive phenomena were encountered. The larger doses of H.S.E. induced a local reaction which closely resembled the lesion of erythema nodosum. The site of inoculation became swollen, tender and even brawny in appearance. No ulceration followed and the visible reaction, starting six to eight hours after inoculation, reached its maximum in twenty-four hours and subsided within forty-eight to seventy-two hours. In no instance did such lesions appear elsewhere than at the site of inoculation. In five other patients generalised reactions were produced in which rise of temperature, tachycardia and a return of flitting joint pains were temporarily present. The reaction passed off in twenty-four to forty-eight hours, but the patient was still sensitive and reacted in a similar manner to further injections.

The general results corroborated the findings of other workers that rheumatic subjects are, as a rule, more frequently sensitive to streptococcal endotoxin than non-rheumatic controls. Although sensitivity was not specific for any one kind of streptococcus, it was demonstrated with greatest regularity by the use of the hæmolytic streptococcal variety. The antigenic constitution of the nucleo-protein is at present unknown, and it may contain one or more fractions. It is therefore impossible to state whether the frequency of reactions to H.S.E. is due to a greater content of an antigen common to all three kinds of streptococcus or to some peculiar specific fraction present in addition to the common antigen. As each of the small group

of cases in which this point was investigated had yielded streptococci of all three kinds on throat swab culture, the increased sensitivity to endotoxin of *Str. hæmolyticus* was not simply associated with the presence of this organism in the throat to the exclusion of other species. On the other hand, cases of acute rheumatism were encountered in which no sensitivity to H.S.E. was demonstrable by intradermal tests. The use of autogenous endotoxin in the smaller series had produced 27 or 84·4 per cent. of positive reactions, whereas the mixed product in the extended series of 105 cases induced 71·4 per cent. Possibly an even higher figure would have resulted from the autogenous endotoxin had it been possible to use it throughout. The occurrence of negative reactors was to some extent corroborative of the conclusion reached by Gibson, Thomson and Stewart (1933) that skin sensitivity could not be regarded as an indication of a special reactivity necessary for the production of rheumatic infection, but it did not detract from the possibility that part of the rheumatic syndrome is due to hypersensitivity. As an analogy, cases of tuberculosis, in both the human and bovine species, may occasionally fail to react to tuberculin despite the recognised part played by allergy in this condition.

A more striking demonstration of the sensitisation of rheumatic subjects to hæmolytic streptococcal products was afforded by the occasional untoward results attending the attempted desensitisation by subcutaneous injection of H.S.E. Localised reactions resembling erythema nodosum and generalised reactions, indistinguishable from naturally occurring relapses but for their transient nature, were thus induced. Although this cannot be regarded as a specific attribute of H.S.E., as similar reactions have been produced by the intravenous injection of vaccines of *Str. viridans* (Swift, Hitchcock and Derick, 1927-28), the delayed type of reaction was distinct from the immediate or rapid response of non-protein shock therapy. The fact that such reactions occurred indicates the need for extreme care in the use of vaccines or bacterial extracts in such patients.

Part IV.—Observations on the Antistreptolysin O Titre in Relation to the Mechanism of Acute Rheumatic Fever

The antigenic nature of the hæmolytic filtrates of streptococcal cultures in serum-free broth was described by Todd (1932*a*), who later (1934) demonstrated the group specificity of the products

and detailed the titration of a neutralising antibody to be distinguished in further work as antistreptolysin O. Todd (1938 *a* and *b*, 1939) found that group A Lancefield (1933) hæmolytic streptococci produce two serologically distinct varieties of hæmolysin, one designated streptolysin O on account of oxygen sensitivity and the other streptolysin S in virtue of extractability in serum. The response in animals to experimental infection with whole cultures of group A hæmolytic streptococci was a rise in titre of the neutralising antibodies, antistreptolysin O (A.S.O.) and antistreptolysin S (A.S.S.). This later work has not rendered less important the application of antistreptolysin O titration in the detection of hæmolytic streptococcal infection.

Todd (1932*b*) first reported the A.S.O. titres of normal human sera to be in the zone of 3-100 units, and demonstrated a rise in titre of varying degree after known streptococcal infections such as scarlatina, erysipelas, etc. Coburn and Pauli (1935*a*) supported these observations by reporting that student nurses before exposure to hæmolytic streptococcal infection had A.S.O. titres of from 33 to 100 units, the mean for the group being 83. In nurses who contracted infection, the titres were later found to range from 117 to 333 units, the mean being 200, while in nurses who escaped infection they remained at the original low level. In a later communication the same authors (1935*d*) noted that the mean of the A.S.O. titres of 176 individuals in good health was 71 units.

On the basis of these and similar results, the titration of A.S.O. has been applied to the study of streptococcal infection in acute rheumatism. Todd (1932*a*) reported a rise in titre during the active stage of rheumatic fever, but considered that this was dependent on the frequent antecedent infection of the throat by hæmolytic streptococci and not necessarily on the intensity of the rheumatic process. Coburn and Pauli (1932) observed a precipitous rise in titre which immediately preceded the appearance of rheumatic manifestations and concluded that the rheumatic attack had been initiated by hæmolytic streptococcal infection. Studying the results of a wave of infection in a group of rheumatic children, all in the quiescent phase with carditis, Coburn and Pauli (1935 *b* and *c*) recorded that 14 out of 16 individuals infected with the epidemic strain developed acute rheumatism, the onset of symptoms being accompanied by a coincident rise in A.S.O. titre. Seven children

who escaped infection also failed to develop acute symptoms and showed no rise in titre. The titres of two patients infected with the epidemic strain remained unaltered, and they also escaped acute symptoms. The median titre developed in acute rheumatism was 500 units and the geometric mean 490.

In comparing the A.S.O. response in different clinical groups of small size, Coburn (1936) found that in scarlatina the maximum titre was reached in seventeen days and in non-rheumatic pharyngitis within ten days, the titres thereafter declining rapidly in both groups. In all rheumatic children who contracted streptococcal pharyngitis followed by rheumatic recrudescence there was an increase in titre. In mild cases this reached its highest limit within nineteen days, but in severe cases the maximum titres were not reached until much later—thirty-four, thirty-six and eighty days after the onset of infection. Coburn was of the opinion that the delay in the appearance of antibody reactions differentiated the rheumatic from the non-rheumatic subject. Further studies by Coburn and Pauli (1939*b*) on the response in non-rheumatic scarlatina and pharyngitis led them to extend the period within which the maximum titre was attained in uncomplicated cases to twenty-eight days. Complications tended to delay the maximum response beyond this period. It was also shown that the prolongation of the immune response affected the anti-M type-specific precipitins as well as antistreptolysin O, pointing to the continued activity of the hæmolytic streptococcus as a whole.

Further data have been presented by Todd, Coburn and Hill (1939), who observed a significant shift to higher figures in the A.S.O. titres of rheumatic subjects who contracted pharyngitis without recrudescence of rheumatism, as compared with non-rheumatic children with pharyngitis or scarlatina. An even greater increase was evident in rheumatic children who relapsed after throat infection.

Similar observations over a period of three years were made in patients, all males, of whom 96 per cent. were in the age group sixteen to eighteen years (Green, 1941*b*). The cases of acute rheumatism under investigation were mainly primary attacks in boys who had passed a certain standard of medical examination not longer than three years prior to the onset of illness. With few exceptions, anyone admitting a previous history of rheumatism had had no other recurrence within that period.

Acute rheumatism manifested itself in the group with the usual symptoms of pain and stiffness in one or more joints, followed by flitting arthritis in a varying number of joints. Marked effusions were not common, but transient swelling and tenderness were present in the early stages. Cardiac complications followed in a considerable proportion of cases. Although the joint symptoms were generally of moderate severity, the cardiac lesions rendered the condition no less serious.

Clinically the cases were arbitrarily divided into monocyclic and polycyclic types. The monocyclic group presented a single phase of activity with pyrexia and joint pains of varying degree and duration, with or without complications. In polycyclic cases, two or more such attacks were separated by less intense periods in which there was some indication of continuing activity.

The range of antistreptolysin O titre during the active and inactive phases of 110 acute rheumatic attacks were grouped according to the extent of the titre range—*i.e.*, the difference between the highest and lowest readings recorded throughout the particular attack. Of the 64 monocyclic cases, 56 were accompanied by a significant change in titre. This figure included 50 cases in which titres during the active phase of rheumatism were higher than in the inactive phase, and 4 in which the titres during inactivity were the higher. No titre below 100 units was recorded in the monocyclic cases with constant titres, 5 being in the 100-249 zone and 3 at 250 units or over.

In the polycyclic series, 43 of 46 cases showed a significant variation. In 38 the active phase titres were higher than the inactive, and in no case were all the inactive titres higher, although significant change in titre occurred without detectable clinical alteration in 5 cases. Of the 3 cases with fixed titres in all stages, 2 were in the 0-99 unit zone and 1 in the 100-249.

Thus 88 of 110 cases showed a response indicative of recent streptococcal infection, 11 failed to react, and 4 cases presented a reversed effect.

From each of 15 cases of scarlatina and 24 cases of hæmolytic streptococcal pharyngitis, a sufficient number of titrations were available to determine the range during active infection and convalescence. In scarlatina, all titres during activity were higher than in convalescence, 11 of the 15 cases exhibiting a maximum variation. Of the 24 cases of pharyngitis, a maximum reaction was noted in only 7, and in 8 cases a moderate increase

occurred during activity. The remaining 9 cases showed no appreciable change, although the titres were over 100. As sera from several of these cases were not obtained until four to seven days after the onset of infection, it is possible that an early reaction was missed.

Healthy Subjects.—The sera from 107 healthy subjects were selected without regard to history of recent pharyngitis for which there were no bacteriological data. The distribution of the A.S.O. titres in this group was such that 88 were less than 125 units and only 3 above 250, the arithmetic mean being 79.

Non-Rheumatic Pharyngitis and Scarlatina.—The combined distribution of these two groups represented a marked shift to higher figures, 107 being over 125 units and 68 above 250, the arithmetic mean being 280. The scarlatina figures were somewhat higher than those for simple pharyngitis, the arithmetic means being 300 and 263 respectively.

Rheumatic Group.—The general effect of rheumatic activity was obtained by comparing the distribution of all sera collected during active and inactive periods. The distribution of titres during quiescent periods was intermediate between that of the normal controls and the non-rheumatic pharyngitis and scarlatina group, but much nearer the latter. The A.S.O. titres of 263 of 398 sera (66 per cent.) taken during the inactive period were 125 units or more, and 138 were over 250 units. With the development of rheumatic activity, the distribution was raised much higher, 629 of 693 sera (90·7 per cent.) being over 125 units and 484 sera (69·7 per cent.) above 250. Whereas in only 13 sera (3·2 per cent.) during inactivity was the titre 625 units or more, the active group produced 158 (22·7 per cent.) at this high level. The arithmetic means of the active and inactive groups were 444 and 210 units respectively.

Pharyngitis in Rheumatic Subjects.—While under observation, 20 rheumatic subjects in the quiescent state contracted hæmolytic streptococcal pharyngitis. Following upon the throat infection, 16 of the 20 patients developed acute manifestations. Seventeen attacks were followed, one subject having two such lapses. The distribution of the titres of 61 sera from this group was very similar to that in the active rheumatic series, as were the arithmetic means. Four patients experienced streptococcal pharyngitis without reawakening rheumatic infection, and in all four there was no rise in A.S.O. titre. Only 18 sera were

available from this group, which were too few for significant comparison. However, in 14 of the 18 sera the titres were less than 250 units and none was above 400.

The results were then grouped according to the degree of clinical activity. Only 12 sera were obtained during the period immediately preceding activity, all being below 400 units, and the mean, 167, was the lowest in any phase of the illness. During increasing activity the distribution shifted up the scale, the mean titre reaching 412 units. The peak was attained at the stage of greatest activity, with a mean of 538 units. Even at this stage, 12 specimens were below 82 units. With diminishing activity, the figures tended to return to lower values, but remained at relatively high levels as compared with those in the quiescent phase. The arithmetic mean in the immediate post-active phase was 363.

The effect of length of time since infection in scarlatina and pharyngitis was then ascertained. From cases of scarlatina only 6 sera were taken in the first six days of the attack. The titres of 5 were less than 125 units, and the remaining titre was 159. In the second week of the illness, 5 of 7 specimens had a titre of more than 125 units, and in the third week the highest distribution was observed, 17 of 26 (65·3 per cent.) having a titre of 250 or more. The figures during the fourth and subsequent weeks showed a commencing regression to lower values.

The distribution in simple pharyngitis approximated closely to that in scarlatina with only minor differences. Thus higher titres were observed at the commencement of the illness, but in the following weeks the distribution was at a slightly lower level than in scarlatina. Nevertheless, the highest distribution was again observed during the third week. This can be correlated with the finding that 9 of the pharyngitis cases started with titres over 100 but showed no increase, whereas all the scarlatina cases responded with a marked increase in titre.

Titration curves in some of the monocyclic cases of acute rheumatism corresponded to those described by Coburn (1936) as typical of the rheumatic state in that the maximum titre was reached after the period of greatest activity was passed and when the sedimentation rate was improving. Abnormally high titres were maintained for weeks, and in some instances for several months, but a final decrease was observed. In other cases, the titres were as high at the onset of the attack as in any

subsequent stage. It could not be stated that only severe cases were accompanied by a prolonged A.S.O. response. On the other hand, all severe cases in which any rise in titre developed presented this to a high degree. As in all other cases in this group, a final fall in titre was observed.

Titration curves in polycyclic cases afforded good examples of the relationship between rise in titre and clinical crises, the clinical cycles being each attended by an advance in titre, although this was not always of the same intensity.

In the scarlatina group, the typical response was an intense but rapid reaction during the second and third weeks. Occasionally maximum titres were delayed till the fourth or fifth week. In pharyngitis there was also considerable variation in response, and no change in titre was noted in nine of the twenty-four cases examined.

There was marked individual variation in this non-rheumatic group after streptococcal infection. No prolongation of the increased A.S.O. titre was seen, although the actual appearance of increase was not apparent in some cases until the fourth or fifth week. The absence of reaction in a minority of cases indicated that a negative result could not be considered certain evidence of the non-occurrence of recent streptococcal infection.

While under observation, 20 rheumatic subjects in the quiescent phase contracted pharyngitis. Four attacks were followed by uninterrupted convalescence, and in all four cases there was no increase in A.S.O. titre. Fourteen of the 18 sera from this group had titres of less than 250. One case was observed through two attacks of pharyngitis, of which only the second was followed by mild rheumatic activity. The first throat infection which failed to stimulate rheumatic infection also failed to produce any increase in titre, but the second attack of pharyngitis was accompanied by a moderate rise, which persisted during the subsequent period of clinical activity.

Further exceptions were sought by noting instances of renewed activity in rheumatic subjects who had no antecedent pharyngitis. While under observation, 10 subjects in whom rheumatic activity had been quiescent for varying periods developed acute manifestations without clinical evidence of pharyngitis. In 7 of these cases, hæmolytic streptococci were isolated from the throat before the onset of symptoms, either for the first time or after a series of negative results, and in 6 of these the attack was followed by

a significant rise in A.S.O. titre. In the remaining 3 cases, hæmolytic streptococci were not isolated from the throat in repeated examination, but 2 of these also showed a significant rise in titre. In this group of 10 cases, rheumatic activity was accompanied by a rise of titre in 8, despite the absence of clinical evidence of pharyngitis before or at the onset of the attack.

The results from the clinical groups were particularly suitable for purposes of comparison in that all the subjects were males in a strictly limited age group of fifteen to eighteen years. The healthy controls were males in a slightly higher age group of eighteen to twenty years. The low A.S.O. values of sera from this group closely followed the results of Coburn and Pauli (1935*a*), the respective means being 79 and 83. Although controls in the sixteen to eighteen years age groups were not available, little difference was to be expected from the distribution found in the older boys, who had been in a similar environment for at least two months before examination. If anything, the readings in younger boys may have been lower on account of reduced opportunities in age-years for infection to have occurred. On the other hand, it may be argued that there did exist environmental differences in the exposure of the clinical groups and healthy controls, resulting in a greater risk of infection so that the initial titres of the former were higher. Apart from the absence of any evidence of such environmental differences, this criticism is countered by the low titres of the scarlatinal and pharyngitis groups in the first week of illness, and by the relatively low titres from a small number of sera from rheumatic patients prior to the onset of activity.

The distribution of titres in non-rheumatic scarlatina and pharyngitis presented, therefore, a marked and significant shift up the scale of values but to a lower plane than that observed by Todd *et al.* (1939). The data indicated that the maximum titre in scarlatina and pharyngitis was attained most frequently in the period fourteen to twenty-one days after infection. Experimentally it has been observed that the A.S.O. titre falls within a few days of supplying the antigen (Green, 1941*a*). From these observations it may be deduced that even in simple pharyngitis and in scarlatina there is prolongation of the antigenic stimulus for a considerable time after the acute throat infection has subsided, but that this does not extend beyond four to five weeks.

Coburn and Pauli (1939*b*) have fully demonstrated that prolongation of the increased titre in scarlatina and pharyngitis was due to complications or continued infection.

The results confirm previous observations on the general increase in A.S.O. titre in acute rheumatism, although the degree of increase was not as great as that reported by Todd *et al.* In presenting the results, two methods were considered essential in attempting correlation with the clinical process. The tabular recording of actual titre values provided a very satisfactory method for the statistical comparison of different groups, but did not disclose the various responses encountered in a single clinical entity. Thus, although, in a recognised infection such as hæmolytic streptococcal pharyngitis, an increase in A.S.O. titre was the general finding, some patients failed to respond, irrespective of the high or low level of the initial titre. No fall in titre, however, was noted in an established infection. As may be expected from the toxigenic nature of scarlatina strains of hæmolytic streptococci, six fully observed cases of this disease presented a well-marked reaction.

The variations in non-rheumatic subjects must be considered when the A.S.O. response of rheumatic subjects is examined. The shift to higher values in rheumatism was confirmed, as was the maintenance of high values for much longer periods than in non-rheumatic controls. Therefore it was surprising to find that six out of seventeen acute attacks in known rheumatic subjects, preceded by pharyngitis of hæmolytic streptococcal origin, were not accompanied by any significant increase in titre. This proportion, it may be noted, was roughly that of the non-rheumatic group, whose titres were also unaffected by pharyngitis. Reactivation of rheumatism, therefore, could not be invariably linked with further increase in A.S.O. titre following repeated throat infection. However, it should be remembered that the distribution of A.S.O. titres in inactive rheumatism was much higher than in normal controls, and therefore the above conclusion did not exclude the possibility of further streptococcal activity which was masked by the high titres already reached. Unpublished observations have shown that in animals with relatively high A.S.O. titres the further injection of large amounts of streptolysin O may have little or no effect. When the variation in non-rheumatic subjects to hæmolytic streptococcal products was taken into account, the evidence in support of such infection

in the majority of the rheumatic group was considerably strengthened. In the absence of direct proof of continued streptococcal infection, Coburn (1936) has suggested that this evidence indicated an altered response on the part of the rheumatic subject to antecedent infection. One difficulty in the acceptance of this view has been stressed by noting that typical attacks recur in known rheumatic subjects without further increase in titre.

Part V.—The Effect of Prontosil Therapy on the Anti-streptolysin O Titre in Rabbits during Immunisation

The mode of action of prontosil and allied drugs has been the subject of intensive research, but there are few records of the effect of such therapy on antibody response, upon which the ultimate success of the treatment partly depends. Although much remains obscure, the general conclusion has now been reached that drugs of this group act mainly by producing bacteriostasis, thereby permitting the natural defences to come into full operation. Without adequate experimental evidence, the suggestion has frequently been made that actual stimulation of these defences by the drugs or their derivatives may also be a factor.

In hæmolytic streptococcal infection, Colebrook *et al.* (1936) demonstrated that, although the addition of prontosil itself to the blood was without effect on bactericidal action, after administration of this drug to animals and man the bactericidal power of the blood for small numbers of organisms was increased. This action was considered to be due to the reduction of the inactive prontosil to *p*-aminobenzenesulphonamide, which had feeble bactericidal powers. These findings have been confirmed, but the possibility of some additional mechanism has been suggested to explain the apparently good therapeutic effect of the drugs. Exploring the possibility of specific tissue stimulation by prontosil, Gay and Clark (1937) could find no evidence, in experimental streptococcal infection in rabbits, that the cell reaction, which finally accounted for the disposal of the organisms, was other than local, and concluded that the spread of infection was prevented by bacteriostasis. Levaditi and Vaisman (1935) recorded in-vitro inhibition of streptococcal hæmolysin by prontosil I (4-sulphamido-2-4-diamino azobenzol) and concluded that certain sulphonamide compounds exerted an antitoxic action. Osgood (1938) also suggested that the drugs of this group inactivated hæmolysin and perhaps other toxic products. Gross *et al.* (1938)

found that prontosil II produced more marked inhibition of streptococcal hæmolysin *in vitro* than did sulphonamide, which had only a slight reaction. They also observed that the administration of sulphonamide *in vivo* and its addition to serum did not enhance the inhibitory action of rabbit serum on streptococcal hæmolysin. On the other hand, Huntington (1938) concluded that the slight delay of hæmolysin production caused by sulphonamide in broth cultures was possibly due to modification of the growth curve. Sulphanilamide was without effect upon the formation of erythrogenic toxin *in vitro* and was unable to inactivate small amounts of the toxin when used in a concentration equal to or greater than that induced in body fluids therapeutically.

In this part of the thesis, observations on the effect of prontosil therapy on the antistreptolysin O response of rabbits were recorded (Green, 1941*a*). This antibody can be accurately titrated, and its production as part of the natural response to hæmolytic streptococcal infection has been fully demonstrated by Todd (1932*a*). Despite considerable individual variation in response the results indicated little if any interference with antistreptolysin O production in experimental animals as a result of the simultaneous injection of hæmolytic streptococci and prontosil. It is to be expected that similar results would be found if other antibody reactions were investigated. The serum of non-immune rabbits under prontosil treatment had no neutralising action on streptolysin O, nor were the antihæmolysin O titres of immune rabbits increased by the treatment.

Apart from the academic interest of the subject, the problem is of practical importance in view of the wide application of prontosil therapy. The use of the drug is often followed by periods in which a focus of infection persists. It is important, therefore, to ascertain if there is any check to the development of the natural defence mechanism as a result of treatment with prontosil. So far as dosage was concerned, the daily injection in these experiments approximated to 0·03 g. of prontosil II per kg. body weight, the total amount injected over a period of twenty-two to twenty-three days being 0·66 to 0·69 g. Neglecting species differences, the equivalent amounts for a 70 kg. man would be a daily dose of 2 g. and a total of 64 to 66 g. Larger doses are commonly used in the early days of treatment to secure a maximum effect rapidly, but there was no necessity for this

procedure in the experimental work, in which it was possible to institute therapy before infection occurred. Experimentally the drug was used at least forty-eight hours before infection, so that any possible interference with antibody production was favoured as compared with human infections, in which the antigenic stimulus has been applied, in most cases, before therapy is commenced. It is a reasonable assumption that prontosil has no appreciable antagonistic effect on antibody production in human infections.

The observations may throw further light on the disappointing results with prontosil in the treatment of acute rheumatism reported by Swift *et al.* (1938). If, as suggested by Coburn (1936), the delayed and precipitous rise in A.S.O. titre after hæmolytic streptococcal infection of the throat is part of the rheumatic process, then prontosil therapy will neither prevent nor reduce the antibody response. On the other hand, the prophylactic use of prontosil in preventing throat infection and thereby eliminating the most common stimulus for increase in A.S.O. titre should be of benefit. Encouraging results for this method of prophylaxis have already been reported by Coburn and Moore (1939). A much more remote question (upon which the work touches) is that of immunisation against hæmolytic streptococcal infection. If it is possible so to develop control of hæmolytic streptococcal infection by means of prontosil that all risk of spread of infection is eliminated or reduced to low limits, it may also be possible to introduce a system of modified infection with virulent organisms for improving passive and possibly active immunisation against certain of the diseases of which this organism is the causative agent.

Part VI.—Rheumatic Carditis: Post-Mortem Investigation of Nine Consecutive Cases

This part was based on a paper published in Annals of the Rheumatic Diseases, 1939, **1,** 86. In brief, the pericardial and valvular lesions in nine cases of acute rheumatic endocarditis were examined bacteriologically. Hæmolytic streptococci were recovered from valves with macroscopic lesions in eight cases, but not from the valves without lesions nor from the heart blood in the same cases. Unless a phenomenal chance distribution of hæmolytic streptococci in the heart valves of the various cases were postulated, the results indicated that agonal or post-mortem

blood invasion did not explain the appearance of hæmolytic streptococci in only valves with macroscopic lesions. Coliform organisms were also isolated under the same conditions, but were found in the heart blood and in cultures from both healthy and diseased valves. Careful examination of serial sections of vegetations excluded the possibility that the positive findings were the result of subacute bacterial endocarditis. The pathological manifestations were entirely those of rheumatic endocarditis, and no organisms were found in sections stained by the routine Gram's method. Any possibility that the presence of hæmolytic streptococci was the result of contamination from some source other than the tissues of the bodies under examination was completely excluded by the fact that in five cases the streptococcus recovered from the cardiac lesion, in the individual case, was of the same serological type as the strain isolated from the patient's throat before death. Further, in those cases where hæmolytic streptococci were isolated from more than one valve the strains were serologically identical. Indirect evidence has already been reported as to the part played by hæmolytic streptococci. These observations greatly strengthened the evidence, although the number of cases in the series was too limited to be conclusive. They were recorded to encourage further work on the same lines, and this was forthcoming.

Part VII.—Results of Animal Inoculation with Pathological Material from Acute Rheumatism

Only two cases described in the preceding part yielded pericardial fluid at post-mortem in amounts sufficient for animal inoculation, some of which proceeded to develop hæmolytic streptococcal infection. In view of the results of valve culture it was important to compare the appearances in the tissues in the experimental animals with those in human tissues (Green, 1939*b*).

In the tissues of the experimental animals from which hæmolytic streptococci were recovered, a peculiar distribution of the organisms was occasionally noted, unlike that usually associated with suppurative lesions due to this group of organisms. There was a tendency for the cocci to be clumped in large masses, the individual members of which were feebly Gram-positive or frankly Gram-negative. Another curious feature was the lack of phagocyte reaction in the vicinity of the bacterial masses.

The conclusions to be drawn from the comparison of human and experimental tissue appearances were not easily made. Certain bodies observed in the human heart sections may have represented degenerated cocci, or an alternative explanation for their presence was that they were derived from the tissues themselves—*e.g.*, mast-cell granules. The differentiation between the two is comparatively easy if the cocci react to staining methods and are distributed in the expected manner. When aggregated into masses morphologically indistinguishable from the coccoid bodies in the human heart sections, differentiation was exceedingly difficult.

At present, final conclusions as to the nature of these coccoid bodies have not been made. In view of the frequency with which streptococcal infection is linked with rheumatism, it is tempting to speculate whether some of these appearances in human heart valves may not actually be due to the presence of cocci, particularly as the cultural results strongly support this conclusion. If that be the case, then they indicate the existence of a peculiar relationship between the hæmolytic streptococcus and the human host. Interesting as this speculation may be, it must await further investigation.

Part VIII.—Epidemiology of Hæmolytic Streptococcal Infection in Relation to Acute Rheumatism

Section 1. *Hæmolytic Streptococcal Epidemic and First Appearance of Acute Rheumatism in a Training Centre.*

The reawakening of the rheumatic process in patients as a result of respiratory infection, particularly tonsillitis, has been fully described by many observers, including Raven (1923), Boas and Schwartz (1926), Hiller and Graef (1928), Schlesinger (1930), Collis (1931), and Coburn and Pauli (1935*c*). Reports concerning the appearance of rheumatism in apparently healthy communities after such epidemics have still further stressed the linkage between the two conditions. Thus Glover and Griffith (1931) and Bradley (1932) described outbreaks in schools after epidemics of hæmolytic streptococcal tonsillitis.

This section described the circumstances under which a similar outbreak occurred in a training centre. Factors which contributed to the outbreak were, firstly, the introduction of a susceptible class of apprentices at a time when the risk of infection

was high. As suggested by Dudley (1926), this probably resulted in an increase in virulence of the infecting organism by passage. Following the increase in virulence the number of clinical infections appearing in a given class varied with age of the class and with the susceptibility of its members. Thus, almost 80·0 per cent. of cases occurred in the younger classes A and B. Contrary to expectation, the ratio of the number of cases of scarlatina to those of tonsillitis in class A was 1 : 1·5 and in class B was 1 : 0·75. This distribution suggested that the members of class A had experienced greater individual contact prior to the epidemic than the older subjects in class B. Dick-testing showed that the influence of the epidemic on the antitoxin immunity of class A was very considerable and within a few weeks produced an effect which would have taken months under normal circumstances. Indeed, the smallest percentage of post-epidemic Dick-positive reactors was found in the youngest class, which had suffered most in the outbreak.

The marked difference in the total incidence of respiratory infections—viz., 51, 19, 12 and 8 in classes A, B, C and D respectively—was a good example of the effect of herd immunity, the class of longest age showing the greatest percentage of survivors, irrespective of the individual immunity.

Acute rheumatism did not appear until the streptococcal outbreak had been in progress for some time and all save one case had been involved, clinically, in that epidemic. Moreover, all cases of rheumatism occurred in apprentices, and, with one exception, in the two classes which were most seriously involved in the epidemic. Environmental features common to all classes, such as dietary factors, climate, physical and mental stress, were thus completely overshadowed by the preceding streptococcal infection.

Section 2. *Epidemic Rheumatism.*

Although multiple cases of acute rheumatism have been observed to follow waves of streptococcal infection, there is doubt as to whether acute rheumatism itself becomes epidemic or whether the element of infectivity lies in the preliminary throat infection as concluded by Sheldon (1931). A large-scale instance of this kind in a semi-closed community was described in this section.

As regards the streptococcal ætiology of rheumatism it was

important to consider to what extent primary infection was encountered as contrasted with a recrudescence of existing infection. It was reasonably presumed that obvious rheumatic stigmata such as marked valvular lesions were eliminated at the entrance examination. Clinical experience has proved that latent infection readily escapes detection at such an examination, no matter how thoroughly it is conducted. However, it was most unlikely that all cases which subsequently appeared were of this type, for an attack rate of 63 per 1,000 was almost certain evidence that primary infections were taking place. Granted this was the case, then the association with hæmolytic streptococcal infection assumed much greater significance. That this correlation was not exact did not exclude streptococcal infection as a primary factor. Considering the ætiology of another disease spread by droplet infection—namely, cerebrospinal fever—the same absence of correlation between known contact with the causative agent and the incidence of cases has been noted. Thus Dudley and Brennan (1934) showed that, in a large community, a carrier-rate of 50 per cent. for agglutinable *N. meningitidis* persisted for over twelve months, but no cases of cerebrospinal fever appeared in the community. On the other hand, in another community with six cases of meningitis, the carrier rate was only 5 per cent. By contrast, Glover (1920) had found that the carrier rate was in the region of 70 per cent. when cerebrospinal fever outbreaks were imminent or present. There is apparently no simple rule governing the relationship between carrier rates and the appearance of clinical cases, the varying factor which complicates the issue being the herd immunity of the exposed population. In this epidemic the rising incidence of throat infections and scarlatina in the first term was an index of the increasing virulence of the hæmolytic streptococcus as a result of passage through the community, culminating in the appearance of multiple cases of scarlatina. Despite the reduction in incidence at the start of the second term due to the dispersal of the population, the epidemic rapidly regained its former strength by reason of the increased virulence of the infecting organism. The elimination of scarlatinal susceptibles was indicated by the lowered figures in the second term. At the start of the third term, the increased virulence of the organism maintained the number of clinical cases at a high level, but an important antagonising factor came into play—namely, the increasing immunity of the community.

Although scarlatina was more frequent in this term, the majority of the cases were in new entries who had recently joined and had not experienced the immunising action of the previous terms. By the summer of 1938, the community was thoroughly saturated with hæmolytic streptococci, and the attack rate was so high that few persons escaped one or more attacks of nasopharyngeal infection. With few exceptions, all those who developed rheumatism had two or more attacks of throat infection before the onset or else the second attack of throat infection coincided with the appearance of joint manifestations.

A marked difference in the incidence of rheumatism and scarlatina in relation to time of exposure to the environment of the institution was demonstrated, which again indicated that a different mechanism was at work. An analogous difference was observed in the incidence of scarlatina and tonsillitis, which was known to be of hæmolytic streptococcal origin in practically all cases. The latter difference was due largely to the variation in antitoxin immunity of the exposed herd produced by the periodic introduction of fresh susceptibles.

Section 3. *Comparative Incidence of Various Infections and Acute Rheumatism in Certain Training Centres.*

Longstaff (1904) drew attention to the fact that waves of streptococcal diseases, such as erysipelas, scarlatina and puerperal fever, synchronised with rheumatic fever. Atwater (1927) came to the same conclusion and, in addition, he noted the correlation between the mortality rates of the same conditions.

Reviewing the position of acute rheumatism in the Forces, Glover (1930) observed that the incidence varied as the pressure on sleeping accommodation. He drew an analogy between acute rheumatism and cerebrospinal meningitis on the ground that waves of acute tonsillitis preceded the appearance of cases of both diseases. Dudley (1926) also noted the effect of overcrowding, but considered that damp and chill were also factors in determining the appearance of rheumatism. This conclusion was based on the fourfold drop in the incidence at a training centre after an improvement in hygiene administration which was specially directed to preventing damp and chill. Other factors demonstrated by Dudley to be of prime importance in influencing the incidence of infectious diseases, including rheumatism, were the rate of change of population occasioned by recruiting and discharging,

and the herd immunity of the community. In Dudley's report Vickery was quoted as observing that the incidence of disease fell more heavily on the newly joined boys. Thus, in 1912, there were 2,949 entries on the sick-list of one training centre, of which 60 per cent. were boys in their first three months, 24 per cent. in the second and 16 per cent. in the last three months of their training. Similar findings have been described in the previous sections, and the subject was then considered on a wider basis by examining the incidence of rheumatism and other diseases in several training centres, which showed marked variation in morbidity rates over the same period of time.

The investigation indicated the complete absence of any relationship between acute rheumatism and epidemics of rubella, measles, chicken-pox, common cold and diphtheria. On the other hand, the distribution of rheumatism was similar to that of tonsillitis. This correlation was not exact, and the difficulties in estimating this were illustrated by comparing the data from five centres. Two of the centres had the same rheumatism rate of 22 per 1,000, but the throat infection rates per 1,000 differed markedly, being 148 and 778 respectively. Yet another centre had a rheumatism rate thrice that of the previous two, but the tonsillitis rate was less than half that of the more heavily attacked. The effect of age on the incidence of rheumatism in training centres was well demonstrated in an institution in which young boys were replaced by trainees aged twenty-one years or more. There was an immediate reduction in the incidence of all respiratory diseases, and only two cases of acute rheumatism were notified as against twenty-two and thirty-seven in the corresponding period of the preceding two years when the younger boys were in residence. The experimental conditions in this case were ideal except that the two groups were in occupation at different times. The climatic conditions were similar in each year, and the evidence indicated that the more frequent occurrence of acute rheumatism during the winter months was due to the simultaneous increase in respiratory infections and not to any influence of climate *per se*. If the usual conditions are reversed and infection becomes more common in the summer, as happened in the epidemic described in section 2, then rheumatism is also more prevalent.

Part IX. — Preliminary Observations on the Use of Convalescent Serum in the Treatment of Acute Rheumatism

In certain communities of young male adults engaged in strenuous physical training there has been a considerable amount of acute rheumatism. In a few individuals there was a definite history of some manifestation of rheumatism before admission to the training centre, but in many the first attack was experienced within a few weeks of entry. The mode of onset was extremely varied. In the majority of cases, nasopharyngeal infection antedated the insidious onset of stiffness and pain in one or more joints which demanded medical attention, and the patient was then found to be febrile. In others the disease appeared with dramatic onset of hyperpyrexia, sweating and polyarthritis, as in typical rheumatic fever. On the whole the joint lesions in this latter group of cases have not been striking. Large effusions were not common, but tenderness, slight puffiness and œdema of surrounding tissues were the usual manifestations. Flitting in character, the joint lesions rapidly improved and left no apparent injury. The initial pyrexia rarely lasted longer than one week irrespective of the treatment adopted, but exceptional cases continued febrile for months. Remissions and relapses occurred frequently, and symptoms were greatly relieved by salicylate therapy. Despite the apparent mildness of infection in the early stages of the disease, the cardiac complications have been all too frequent, and have occasioned great anxiety on account of the resulting incapacity. Fortunately, a number of patients did not show any tendency to develop cardiac lesion. As these were otherwise healthy young adults, it was decided that serum, taken from such patients during convalescence, should be tried in the more acute phase of the disease in subsequent cases.

This part records the results of a preliminary investigation (Green *et al.*, 1940) on the use of convalescent serum from such patients in the treatment of acute rheumatism. As far as possible, no form of treatment other than general nursing and local therapy was used in conjunction with serum. In 10 cases, no salicylates or allied preparations were used throughout the illness. Of these, 7 cases reacted favourably to the treatment. Given in the early stage of the disease, the use of serum was followed by a rapid fall in temperature and speedy relief of the symptoms.

Six of the 7 successfully treated cases were primary attacks, and the seventh was a recurrence. No case has relapsed since treatment, and all have returned to duty. Three cases of this group did not react favourably to serum. In this group of 10 cases, 9 have now been at duty for months without relapse and with no evidence of permanent cardiac damage. The remaining case has a valvular lesion, but tolerance has been good and he is also back on duty. In 5 cases serum was used in combination with or as an alternative to salicylates. Three subjects in this second group have returned to duty without carditis. One patient was discharged with both mitral and aortic lesions, and one patient has returned to duty with a mitral lesion.

Clinical study of the cases has left no doubt that arthritic pain was relieved, and, of the 15 cases treated in all, 9 were considered to have benefited. Other antisera have been used in the treatment of rheumatism. Thus antistreptococcal serum has been tried with varying success. Wilson (1930) and Hill (1928) reported adversely on its use, while Toogood (1926), Easson and Thomson (1934), and Small (1928) were of the opinion that serum was of value.

The volume of serum available for the present investigation was not large enough to permit really adequate dosage in every case, but the results obtained justify further extension on the lines suggested. One point which will require careful investigation was the occurrence of partial collapse in two individuals within a short period of receiving an injection of serum. The cause of this peculiar phenomenon has not been discovered. Anaphylaxis was considered, but the time relations did not appear to support this possibility. That it was not due simply to repeated dosage has been shown by the absence of any untoward reaction in patients receiving similar courses. Nor could any individual batch of serum be incriminated since two separate batches were concerned, and other patients treated with the same sera had not been affected. Similar reactions have been reported by Hitchcock, McEwen and Swift (1930), following the use of antistreptococcal serum, and by Poynton and Schlesinger (1937). In their cases the serum was obtained from heterologous species, whereas in the present series the serum was from the homologous species. Alarming as these two incidents were at the time, they do not present a serious contra-indication as the patients rapidly responded to appropriate treatment.

It is hoped that the investigation will be extended, and that the true value of serum therapy will be ascertained by its effect on the course of the disease and, in particular, on the prevention of cardiac lesions, when given in adequate doses in the early stages of arthritis.

Part X.—Reactions Induced by Intradermal Injection of Rheumatic Joint Fluid: Neutralisation by Convalescent Sera

Although acute rheumatism is frequently associated with streptococcal infection, the joint fluid in rheumatic arthritis is usually found to be sterile. Of the exceptional observations may be mentioned the work of Richards (1920), and of Billings, Coleman and Hibbs (1922), who reported the isolation of streptococci in cultures of joint fluid. Cecil, Nichols and Stainsby (1929), in addition to recovering attenuated hæmolytic streptococci from blood cultures in a large series of cases, found the same organism in some of the joint lesions. Examination of stained smears of joint fluid shows, in the main, polymorphonuclear leucocytes in various stages of destruction. Organisms can rarely be detected, but the occasional finding of Gram-positive cocci has been reported by Graff (1936) and by Poynton and Schlesinger (1937). Clinically the joint pains in acute rheumatic fever are fleeting in character, and the joints are rarely left with permanent damage after the initial attack. In these respects the arthritic lesions appear to be due to some transient toxic action rather than the result of actual tissue invasion.

In the previous part it was shown that convalescent serum had a beneficial action when given to certain cases of acute rheumatism but was without effect in others. This part deals with an attempt (Green, 1940) to find the mechanism of this action, and thereby to formulate a method for the selection of sera for therapeutic purposes.

The evidence suggested the presence of some toxic or irritative component in the joint fluid from three cases of acute rheumatism, the three specimens being sterile as judged by the cultural tests adopted. The appearance of an erythematous reaction produced by the intradermal injection in a volunteer was very similar to the Dick reaction. The erythematous reaction was demonstrable in the human subject and not in rabbits nor in guinea-pigs—a fact in accordance with the observation that rheumatic fever

cannot be transmitted experimentally to lower animals. So far only one subject has been tested for reactivity to these joint fluids, and there have been no untoward sequelæ. As regards the properties of the toxin-like component, little information has been obtained because of the difficulties in working with a fluid of high protein content. Storage at 6° C., followed by incubation at 37° C., caused some deterioration.

The observation that sera in the later stages of convalescence developed the capacity to neutralise the action of the fluid, whereas this did not occur at the onset of infection, gave further support to the hypothesis that a toxin-like component was present. The neutralising action of sera during convalescence was demonstrated in two of the three cases studied, and its appearance coincided with the clinical improvement of both patients. The third case was of much greater severity in that pericarditis supervened and no neutralisation effect was demonstrable at any time that the patient was under observation. Alternative explanations for the appearance of the reaction were, firstly, that it represented a non-specific effect. If this were the case, then the neutralising action of the serum, absent in the acute phase of illness and appearing only in convalescence, was a curious phenomenon. Secondly, although the joint fluids were sterile in the ordinary sense, they may have contained a living agent which required growth factors other than those supplied in the media used.

It is opportune, at this stage, to review the recent work on the virus ætiology of acute rheumatism. The presence of a particulate agent of the nature of a virus in the pericardial and pleural exudates from acute rheumatism was concluded by Schlesinger, Signy, Amies and Barnard (1935), on the ground that suspensions of these particles were specifically agglutinated by sera from resistant cases of acute rheumatism but not by sera from normal persons nor even from closely allied conditions such as rheumatoid arthritis. These observations were generally confirmed by Eagles, Evans, Fisher and Keith (1937), who unsuccessfully tested the infectivity of the suspensions in monkeys. Completely negative results of transmission experiments by Schlesinger and Signy (1938) have since appeared. Van Rooyen, Green and Sclater (1937) were unable to confirm the serological findings reported above, and Eagles and Bradley (1939) have concluded that it was questionable whether the

agglutination of particle-suspensions, which they elicited equally well (in approximately 40 per cent. of specimens) with sera from rheumatic fever, arthritis of the rheumatoid type of unknown ætiology, or arthropathies not classified as rheumatism, could be accepted as undoubted evidence that these suspensions contained virus elementary bodies. Apart from the evidence of serological and animal transmission experiments, the distribution of acute rheumatism in semi-closed communities described in this work did not conform to that of any of the known virus diseases. The latter were characterised by sharp explosive outbreaks, whereas cases of rheumatism were more uniformly distributed in relation to time. Furthermore, the author has made extensive use of the technique of chorio-allantoic membrane inoculation of the developing egg with entirely negative results. This technique was initially adopted in an attempt to repeat the work reported by Swift and Brown (1939) on the isolation of pleuro-pneumonia-like organisms from rheumatic exudates. In the following year (1940) the same authors withdrew their claims.

The properties of the toxin-like component in the joint fluids were not ascertained, although the presence of neutralising antibodies in the serum during convalescence indicated its probable antigenic nature. On this account, reference must be made to the description by Coburn and Pauli (1939*a*) of the appearance of a precipitogen in the serum, prior to the onset of acute rheumatism. The nature of the precipitogen was not identified, but it was suggested by the authors, following the work of Hughes (1933) on yellow fever, that it may have represented a secondary antigen, resulting from the delayed interaction of streptococcal products and circulating antibodies. If this were the case, then the precipitogen was unlikely to be related to the agglutination of virus-like particles, for Eagles and Bradley (1939) showed that the latter phenomenon did not run parallel to the antistreptolysin O titre. A relationship cannot be completely excluded on these grounds, for Todd, Coburn and Hill (1939) have reported that the antistreptolysin S titre tended to be low when the clinical symptoms were most pronounced during rheumatic attacks, whereas the antistreptolysin O titre was then maximum. Coburn (1940) has emphasised that the low antistreptolysin S response was the only exception in a number of tests which revealed streptococcal activity in rheumatism.

Part XI.—The Formol-Gel Reaction and Erythrocyte Sedimentation Rate in Acute Rheumatism

This part, based on the paper published in Annals of the Rheumatic Diseases, 1939, **1**, 180, was included as a recognition of the valuable assistance which this non-specific test afforded when attempting correlation of clinical activity with serological findings. The insidious onset of cardiac complications in certain cases of acute rheumatism may baffle the most careful observer, but the above tests served to date the recurrence of activity with few exceptions. According to Lloyd and Paul (1928) the formol-gel test was directly influenced by the globulin/albumin ratio, and positive results indicated a relative increase in circulating globulin. Bradley (1938) has shown that there was an absolute increase in the volume of plasma in acute rheumatism, and suggested that there was a qualitative difference in the proteins. The formol-gel test, therefore, is a useful routine measure, although its non-specific nature must be remembered in the interpretation of results.

Summary

Although the association with hæmolytic streptococcal infection has been fully demonstrated in the relevant part dealing with the throat flora, allergic state, antistreptolysin O titre, and epidemiology of acute rheumatism, the relative infrequency of the latter is at once apparent. This discrepancy would appear to indicate that factors other than infection are also involved in determining the distribution of rheumatism. Read, Ciocco and Taussig (1938) found that the frequency of rheumatic manifestations was significantly higher among the near relatives of a series of children affected with rheumatic disease than among the corresponding relatives of a control series of non-rheumatic children. Gauld, Ciocco and Read (1939) continued similar investigations, and suggested that hereditary constitution may play a rôle in the predisposition to rheumatism. Roberts and Thomson (1934) were of the same opinion, although the incidence of the disease in the brothers and sisters of the series they described was small. Recent work has therefore supported the claim for a strong familial and hereditary tendency to rheumatic fever. Wilson and Schweitzer (1937) go so far as to consider that this tendency is transmitted as a Mendelian recessive character. Other conditions which undoubtedly affect the incidence are

those which accompany poverty, such as unsatisfactory housing and dietary defects. These restrictions limit the incidence of rheumatism to a fraction of the total figure for streptococcal infections, irrespective of the mechanism which directly precedes the onset of rheumatism. As to the actual nature of this mechanism there is a considerable difference of opinion. One theory postulates that an unknown virus is an essential contributory factor, and the evidence in support of this hypothesis has already been discussed. An alternative theory is that recently summarised by Coburn (1940) in which an abnormal response to hæmolytic streptococcal infection is considered to be the differential characteristic of the rheumatic state. This abnormality consists in delayed, inadequate response to the primary throat infection, with the result that viable organisms remain in inaccessible tissues after the healing of the primary focus. Concurrently, sensitisation of the individual occurs, with retention of antibody within the cells of the reticulo-endothelial system. Subsequently the surviving organisms release more antigen into the circulation, and either the primary antigen or a secondary derivative is phagocytosed by the sensitised cells. Contact of this antigen and residual antibody within the cells gives rise to a reaction which stimulates the release of large quantities of globulin into the circulation. At the same time an intense inflammatory reaction and changes in vascular permeability are induced in the tissues, which then become infiltrated with wandering cells, and so give rise to the typical pathology of acute rheumatism.

The investigations described in the thesis gave strong support to the latter theory with certain reservations. Thus the evidence of streptococcal infection was obtained in the majority of cases, and an abnormal response was demonstrated. Furthermore, the survival of hæmolytic streptococci in the absence of a pyogenic focus was noted in some cases of acute rheumatism with fatal termination. There were two points upon which further investigation is required. Firstly, there was no evidence of streptococcal infection nor of an abnormal response in a minority of cases of acute rheumatism. Secondly, the toxin-like component in the joint fluid in the stage of acute arthritis finds no place in the sensitisation theory unless it represents a form of secondary antigen.

In conclusion, then, it is essential that hæmolytic streptococcal

infection should be placed first and foremost in all questions relating to the spread and reactivation of acute rheumatism, but the problem of ætiology cannot be considered as finally solved.

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GENERIC AND SPECIFIC INFLUENCES OF NUTRITION IN THE TOTAL SUPPORT OF ARTHRITICS*

By RALPH PEMBERTON and C. WESLER SCULL

Studies of patients with chronic arthritis reveal that they have disturbances not only in the joints but also in the major systems of the body. It is conceivable that the systemic manifestations of the disorder are referable to deviations of function secondary to some central factor. Information on this possibility, however, is not sufficiently well developed to establish such an hypothesis as fact. In any event the clinical syndrome of arthritis cannot now be regarded as a symptom-complex produced by a single extraneous agent or agency, such as infection. It is, indeed, recognised that many factors are operative in bringing about the syndrome. It appears reasonable, therefore, at least for the present, to consider the disorder, not as a consequence of a partial attack by a single ætiologic agent, but rather as a resultant of the cumulative effects of a "total war" waged by various contributing factors, with varying emphasis, respectively, upon and in the body as a whole. Any therapeutic regimen to be regarded as satisfactory must, therefore, combat not only one but all of the impinging destructive agencies. Measures directed toward single deviations characterising the disease (that is, partial support) are usually inadequate, except by chance. Active intervention must proceed against all directly destructive or subversive influences within the body, such as physical fatigue, anæmia, nervous or endocrinous imbalance, faulty nutrition, postural defects and focal infection. In short, a programme of therapy to be effective must involve "total support" of the patient. "Total support" implies and may be defined as a correlation of various therapeutic procedures which, applied singly, may be of slight avail in arresting the disease, but when applied in co-ordination and appropriately are of great and apparently unappreciated value.

Added significance attaches to the conception of "total support" of the arthritic in that the doctrine of focal infection,

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important though it be, has undergone, at least in the United States, a revision downward. Depreciation of this factor as the main ætiologic and therapeutic influence in arthritis necessitates, as a consequence, fuller recognition of the many factors operative, at least in a contributory way, in the symptomatology of the disease.

While such considerations may appear self-evident to the thoughtful observer, certain of them are inadequately evaluated. This is especially true of nutritional factors. These should be considered, however, not as isolated independent factors but as interdependent components of the whole situation and some reference to elemental principles of nutrition will be necessary in order to present specific recommendations concerning them in proper perspective. "Total support," as defined above, postulates aid to the dysfunctioning systems of the body and, as regards the present thesis, optimal supplies of raw materials for tissue reconstruction. However, the matter cannot be disposed of by so simple a definition and it is not enough to prescribe a well constituted diet. For example, the alimentary tract is often the site of dysfunction, which may condition the efficiency and availability of any diet, however optimal. Again, nutrition is not a function of the gastro-intestinal tract and food alone, and it is commonly overlooked that the finer vascular and lymphatic radicles largely constitute the sites at which nutritive and indeed most vital physiological phenomena actually transpire. Indeed, the larger vessels of the vascular system serve only to bring the fluid to the fixed tissues. The finer vascular and lymphatic channels are usually more or less disturbed in the arthritic syndrome, and it is, by definition, essential in a teleologic sense that the above several systems achieve and maintain optimal function if essential materials are to reach the tissues which need them. These relationships are emphasised because they illustrate an interdependence of various major functions which must be served if the concept of total support is to be actually achieved. Certain specific individual ends are also to be served by adjusted alimentation, but it is not as a single measure, intended alone to control certain phases of the clinical problem, but, also, as an important feature of the several essential parts of "total support," that dietetic regulation should be included in the therapeutic regimen for arthritics. In the opinion of the writers the principles underlying treatment of the

arthritic syndrome are essentially similar for both great types. This statement is not to be interpreted too literally: thus, rest to the atrophic (rheumatoid) arthritic, if improperly conducted, may lead to ankylosis, whereas rest to the hypertrophic (osteo-) arthritic never does. However, rest is nevertheless essential in the treatment of each type. It may be remarked here that some years ago the American Committee for the Control of Rheumatism openly proclaimed its view that arthritis, including both great types, is a systemic disease with joint manifestations. Hypertrophic (osteo-) arthritis of purely traumatic nature, such as the tennis elbow, is obviously not included in the above generalisation. The process of atrophic arthritis (rheumatoid) is supposed to partake of an " inflammatory " nature, and hypertrophic (osteo-) arthritis of a " degenerative " nature, but it is possible to place undue emphasis upon the separation of these two types. Degenerative processes involve factors which are poorly understood and may be no more than the manifestations in later life of factors which in earlier life induce youthful types of reactions.

A further consideration in the application of nutritional regulation to the syndrome of " rheumatism " is that the symptom-complex of arthritis is not always the same in patients presenting rheumatic complaints. The qualitative nature and quantitative extent of nutritional imbalance vary widely. This situation requires an appraisal of the individual nutritive state in each patient. Those practitioners who, on *a priori* grounds, accept no measure as significant unless it is equally applicable to all cases, naturally regard such efforts toward optimal nutrition as a waste of time. It is to be noted, however, that " economy of hypothesis " is permissible only where the members of a class under discussion are alike in all particulars—*i.e.*, are fully described by a single variation from normal. Even the most superficial survey of any large group of atrophic or rheumatoid arthritics reveals extreme variations in clinical and pathological patterns. The maximum benefit from dietetic control can be secured only when such control is directed toward specific as well as toward generic objectives. The prescription of a " good diet," like the prescription of rest, without bearing in mind the favourable or unfavourable influence of the components of rest, may wholly miss the intended mark.

The inter-relationship between nutritive needs and physical activity is one of the most clearly established principles of bio-

chemistry, and the importance of nutritional deficiencies is becoming more generally appreciated. The clinical implications inherent in the above principles are often ignored, however, and patients are sometimes advised to keep physically active while following restricted rations. The influences of over-alimentation are even less widely recognised, and the error of placing a patient in bed and over-feeding him is not uncommon. This has been exemplified, not infrequently, in the treatment of patients with pulmonary tuberculosis.

Under ordinary conditions of good health the disposal of surplus materials does not present a serious problem. However, the tissues of the arthritic are often already the site of surfeits in the form of extra fluids and other tissue " detritus ". Furthermore, the alimentary tract is often atonic as a whole. The gastric secretion is frequently hypochlorhydric, the gall-bladder may be sluggish, and the colon is often enlarged. A recent roentgenographic study (Spackman, E. W., Bach, T. F., Scull, C. W., Pemberton, R., " Complete Roentgen Ray Studies of the Gastro-Intestinal Tract in 400 Arthritics," *Am. Journ. Med. Sc.*, 202, [July] 68, 1941) of the gastro-intestinal tract in 400 arthritics revealed evidence of deviations from normal structure or function of the stomach, gall-bladder and small intestine in 60 per cent. of the cases. The most notable abnormalities were encountered in the colon, 80 per cent. of the cases presenting a pattern of ptosis, dilatation and/or atony. While the full significance of these abnormalities is not yet clear, there can be no reasonable doubt that the margin of functional efficiency involved is smaller than in the normal subject. The absorption and disposal of surplus foodstuffs by an overtaxed organism creates unnecessary demands in the form of extra physiological work, a cost which the already fatigued and dysfunctioning organism can ill afford.

These considerations are of more than academic interest, as can be seen from the experience of one of the writers' patients. This subject, a young male atrophic spondylitic, was brought to a state of symptomatic equilibrium through a balanced programme. After a period of clinical quiescence the caloric value of the diet was increased by 350 calories. A mild exacerbation followed this change in the patient's regimen. A reduction to the lower basal level was followed by a remission in the symptoms of pain and stiffness. Further comparatively precise adjustments of the caloric intake were uniformly charac-

terised by the same sequence of exacerbation and remission. While only a few cases in the writers' experience have shown the same critical response to a small caloric adjustment, many have presented equally dramatic symptomatic responses to brief periods of sharply reduced caloric intake. Clinical exploitation of this relationship is most favourable, and should be conducted only when the patient is at rest in bed and all accessible contributing factors have been cared for. Operation of the influences involved has been widely recognised in the dramatic but ephemeral improvement which, chiefly because of the necessarily lowered food intake, often follows major abdominal operations.

Extended and uncritical use of sub-maintenance diets may lead to unhappy results. A certain American physician, recently deceased, developed a wide following among the laity in both the U.S.A. and England, largely upon the basis of the clinical benefits following restricted dietaries—applied, however, without adequate discrimination as to the eligibility of the patient for such nutritional strains. Another sub-maintenance dietary practice is a so-called "Hollywood" diet, recommended as a reducing programme, and rheumatics are alleged to be relieved of their stiffness and pain by this measure. Whatever other factors may be operative, allegedly or otherwise, the individual improvement experienced by some followers is undoubtedly due to the curtailment of calories with a necessarily attendant release of tissue surfeits. However, the general application of such measures, indiscriminately and without consideration of the complete clinical situation, is wholly unwarranted and hazardous. The orthodox profession is to be blamed if, by indifference to significant physiological influences, it drives the laity to unscrupulous practitioners who apply these influences unwisely. Indeed, the origin of such cults as osteopathy, cheiropraxy, and the like is to be found in comparable obloquy by the profession towards limited but basic influences in the field of physical therapy.

As a practical empirical approximation, the caloric value of the diet for the non-febrile arthritic patient of essentially normal weight at rest in bed is placed at 10 per cent. over the calculated basal energy output. For the ambulatory patient such a restricted intake would lead to caloric imbalance and loss of weight. For the grossly underweight patient, or the patient who is febrile, this quantity would be inadequate. Adjustments of the calories to meet such necessities must be made.

The patient with rheumatic disease presents several features which emphasise the importance of directing special attention to the amount and quality of proteins in the dietary. The atrophic (rheumatoid) arthritic often presents evidence of a systemic deficiency of protein. The muscles are atrophic or wasted. Whether this condition arises from increased demands for protein materials or from disuse, a term which merely indicates an involuntary but purposeful loss of metabolically active material, makes no practical difference. Furthermore, impaired skeletal integrity in arthritis is often evidenced by decreases in inorganic salts, and it seems probable that demineralisation is secondary to changes in the organic matrix of bone which consists largely of proteins. This possibility is suggested by observations by Clark on the X-ray diffraction patterns of the bone matrix in animals with rickets. These diffraction patterns are distinctly different from normal. No direct data on the diffraction patterns of arthritic bones have been recorded so far as the writers are aware.

In addition to the foregoing evidences of protein imbalance in the arthritic, subnormal quantities of cystine in the fingernails have been observed. While this deviation is by no means confined to patients with arthritis, it does reflect some disturbance of nutrition of these structures. It may be observed incidentally that attempts by the writers to produce evidence of articular damage by feeding to rats diets extremely low in lysine and cystine have been negative. Such experiments, however, do not demonstrate that deficiencies of amino acids do not contribute to arthritic pathology.

The fluid tissues likewise present evidence of disturbances in protein metabolism. Many patients, particularly severe atrophics (rheumatoid cases), show marked anæmia. The pathogenesis of the associated anæmia in the arthritic is not fully clear. It appears likely that the reduced number of cells in the peripheral blood is in part a consequence of the disordered bone marrow from which springs the granulation tissue and endosteal activity characteristic of atrophic (rheumatoid) arthritis. While this anæmia is " secondary " in one sense, efficient restoration of the hæmoglobin level depends upon an adequate supply of dietary protein of good biological quality. Similarly patients who have been ill for prolonged periods often present a lowered level of plasma albumin. This reduced level of albumin is partially, though not wholly, responsible for the tendency toward a low-

grade generalised œdema shown by these patients. While the low plasma protein is probably to be attributed to "toxic" influences rather than a primary dietary deficiency, the most efficient means of restoring toward normal this situation centres around a sufficient supply of the raw materials from which albumin is elaborated.

Contrary to a still popular belief, arthritics, except for the few who have gout, show no evidence of a disorder in purine metabolism. There is thus no reason for limiting the supply of nucleoproteins. Neither is there any substantial reason for excluding red meats from the diet of the arthritic. In order to secure the most satisfactory supply of amino acids the protein component of the diet should be secured from a variety of sources. Not less than 1 gram of protein per kilogram of body weight is desirable for the average arthritic patient. For the severely malnourished subject the amount provided should be larger.

The carbohydrate fraction usually provides a large proportion of the calories in the average dietary, especially in the less favoured classes. The influence of excess or inadequacy of carbohydrate is usually regarded as limited to questions of over and under weight. Apart from this generally recognised relationship, however, divergent views are expressed as to the best level for this dietary factor in the regimen of the arthritic. On the one hand it is alleged that the arthritic can ingest a "high" carbohydrate diet without handicap, inasmuch as the respiratory quotient of the arthritic is normal, thus indicating a normal capacity for the oxidation of carbohydrate. On the other hand there is strong clinical evidence to suggest, and there is also strong physiological justification for the view, that the rate of convalescence of certain arthritics may be accelerated by diets comparatively low in concentrated carbohydrate foodstuffs.

A number of dietaries have been employed as part of the treatment of arthritics which differ from average rations in several particulars. Dorothy Hare (D. C. Hare, *Journ. Amer. Med. Assoc.*, London Letter, 1937, 1108, 308) employed a diet consisting of raw vegetables of low sodium chloride content and including approximately equivalent amounts of fats and carbohydrates. Significant clinical improvement was noted in eight of twelve patients under this regimen. A somewhat similar dietary programme has been advocated by Gerson (M. Gerson, *Münch. Med. Wchnschr.*, 1930, **77**, 967). Both Gerson and Hare

attribute the benefits derived by their patients to the low sodium content of the foods. Hare further believes that the comparatively high amounts of vitamins B and C contribute to the favourable influence. Pevsner *et al.* (M. J. Pevsner, B. T. Talalaev, G. L. Levin, J. J. Bouten, A. J. Lacharova, Appendix, *Acta Rheumat.*, 1934, 2021, 7) have employed low carbohydrate diets, composed chiefly of vegetables, with beneficial results which they attribute to desensitising influences. It is to be noted, however, that these dietaries are characterised by under-maintenance or mere-maintenance levels which have certain necessary consequences, to be discussed presently.

The interdependence of specific nutritional factors has been shown by Cowgill (G. R. Cowgill, " The Vitamin B Requirement of Man," Yale University Press, New Haven, 1935), who demonstrated that vitamin B requirement is quantitatively related to the total energy turnover. Not only the absolute but also the relative demand for vitamin B is raised with increased energy expenditure and increased caloric intake. Whether the primary cause for the elevation of energy turnover is a pyrogenic factor or simply an elevation in physical activity, makes no difference so far as the increased need for vitamin B is concerned.

The clinical corollary of this principle has been clearly stated by Spies (T. D. Spies, D. P. Hightower, L. H. Hubbard, " Some Recent Advances in Vitamin Therapy," *Journ. Amer. Med. Assoc.*, July 27, 1940, **115,** 295), in respect to the remission of symptoms and disorders arising from nutritional deficiencies, such as pellagra: " in many cases lesions heal following rest in bed." In addition to the clinical evidence of improvement following reduced physical activity and caloric exchange, Spies and his colleagues have observed that even when a diet remains inadequate with respect to certain components of the vitamin B complex, rest in bed is followed by an elevation of the concentration of coenzymes in the blood.

It is evident that carbohydrates are not to be regarded as harmful *per se* to arthritics. However, there are clear-cut indications in the case of arthritics for keeping the carbohydrate fraction within certain limits. The first of these is a fortuitous one. Concentrated carbohydrate foodstuffs carry very small or negligible amounts of vitamins and minerals. When purified carbohydrates are extremely high in a diet it becomes difficult to secure an adequate vitamin intake from other foodstuffs.

The second indication for keeping the carbohydrate fraction within certain limits depends upon the unfavourable influence of excessive amounts of carbohydrate upon the low-grade œdema of the arthritic, to which attention has been directed by Scull and Pemberton (C. W. Scull, R. Pemberton, "The Influence of Dietetic and other Factors on the Swelling of Tissues in Arthritis," *Ann. Int. Med.*, 1935, **8**, 1247). A significant control of this œdema can be effected by keeping the carbohydrate fraction at a comparatively low level. In this respect a low carbohydrate diet exerts an influence comparable to that of a low sodium

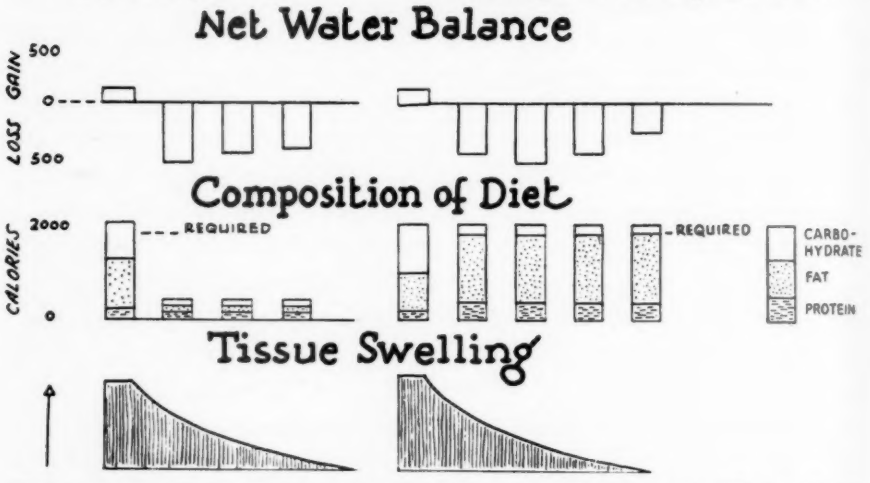

DIAGRAM SHOWING EFFECT OF SOME DIETARY FACTORS ON WATER LOSS AND TISSUE SWELLING IN ARTHRITIS.

Representative data on metabolic studies of arthritic patients showing that tissue swelling may be reduced during periods characterised by losses of water from the body. This may occur with sub-maintenance feedings or on diets which are calorically adequate but in which the proportions of fats and proteins to carbohydrates are comparatively high.

chloride diet. Carbohydrates, when stored or retained in the body in the form of glycogen or glucose, hold four times their weight of water. Fats hold only one-tenth and proteins are stored only exceptionally.

In view of these several considerations it appears desirable in most cases to supply from one-third to one-half of the calories in the form of carbohydrates. Furthermore, it is generally advisable to supply the bulk of the carbohydrates in the form of vegetables and fruits which contain not more than 15 per cent. of this foodstuff. This latter provision helps to assure an adequate

intake of vitamins. Exceptions to these generalisations will be pointed out in the subsequent text.

The remainder of the caloric quota in the dietary of arthritics is of course to be derived from fats, which should afford from one-half to two-thirds of the total calories. From the standpoint of the conditions usually presented by arthritics, this adjustment of the three foodstuffs provides certain desiderata. The above diet is not sufficiently high in fat to be ketogenic, but it does tend in this direction and thus further counteracts, to this extent at least, the low-grade œdema of the arthritic. Furthermore, there is exercised an appreciable sparing action on the demands for vitamin B. Fats bearing appreciable amounts of fat-soluble vitamins should be chosen, such as butter and lard, not only because of these important materials but also because of their content of essential unsaturated fatty acids. There are few arthritic patients unable, because of limited gastro-intestinal function, to handle diets of this high fat content. When this is the case, however, digestive disturbances prevent the beneficial metabolic influences and such diets are then contra-indicated. In addition patients with gout are alleged to undergo exacerbation following the ingestion of large amounts of fat. Except for these comparatively small groups a diet moderately high in fat is usually well suited to the needs of the patient. While hypertrophic arthritics frequently present elevations in the level of cholesterol in the blood, this in itself does not provide sufficient grounds for keeping the fats at a low level.

At the possible risk of stating what may appear to be axiomatic in the rôle of accessory food substances, it is desirable to review at this point a few relevant factors which may have large significance in therapy. There is no evidence that any class of arthritics has its complete origin in a deficiency of any one of the known accessory foodstuffs, but there are certain symptoms which may conceivably have their origin in such deficiencies.

While evidences of deficiency of vitamin A do not dominate the symptom-complex of arthritis, there are clinical indications for the administration of liberal quantities of preformed vitamin A in the programme of total support. The hepatic dysfunction observed among atrophic arthritics* emphasises the necessity

* J. S. Davis, "The Liver an Etiologic and Therapeutic Factor in Certain Types of Blood Disease and in Gout and Gouty Arthritis"; Proc. A.R.A., *Journ. Amer. Med. Assoc.*, 1941, **117** (November), 1147.

for providing vitamin A rather than its precursor the provitamin carotene.

Symptoms conceivably referable to vitamin B deficiency are encountered with considerable frequency among arthritics. A lack of appetite with decreased gastro-intestinal motility is notably common. Symptoms suggestive of peripheral neuritis may be present. The low-grade peripheral œdema above described may be due, in part, to the same mechanism that leads to the œdema seen in wet beri-beri. The ptotic and atonic colon of the arthritic mentioned earlier in this text has been regarded by Fletcher (A. A. Fletcher, *Journ. Lab. and Clin. Med.*, 1930, **15,** 1140) as probably due to a deficiency of vitamin B. These several deviations have often yielded to adjustments of the physiologic demands by means of rest, the reduced total caloric turnover, and the low carbohydrate, high fat diet referred to in the afore-mentioned text.

The connective tissues of the arthritic show a generalised laxity, which may be related to vitamin C deficiency. The gums of arthritics are quite frequently the site of infection; the gingivæ are swollen, tender and spongy. While this situation involves infective factors, it is possible that the infection is in a sense secondary to disordered physiology of the tissues. Muscular weakness and tenderness is another symptom of many arthritics which may conceivably be induced by a relative deficiency of ascorbic acid.

It is notable that arthritics show on the average lower than normal values for ascorbic acid in the blood. Furthermore, larger quantities of ascorbic acid are required by many atrophic arthritics than by normal subjects to increase the renal output over basal levels. Following the ingestion of vitamin C these subjects show a lesser rise in the level of ascorbic acid in the blood than do normal subjects. This increased tolerance or decreased level of tissue saturation is not pathognomonic for arthritis, but may be present when the basal supply of vitamin C is on a level adequate only for the normal subject.

In addition to these clinical data, Rinehart (J. F. Rinehart, *Annals Int. Med.*, 1935, **9,** 586) and his associates have observed lesions in experimental animals maintained upon sub-optimal supplies of vitamin C, bearing a remarkable similarity to those found in atrophic arthritis. While pathologists are not all agreed that the features of the experimental syndrome are identical with those of the clinical variety, there can be no

reasonable doubt that the primary tissue defects arising from vitamin C deficiency could " pave the way " for the development of many aspects of the arthritic syndrome.

The symptom of skeletal atrophy or demineralisation is conspicuous in atrophic arthritis. Attention has therefore been directed to the possible rôle of vitamin D. Recent claims as to the specific efficacy of extremely large doses of modified sterols related to vitamin D in the treatment of arthritis have not been widely substantiated and rather lie outside the realm of nutritive considerations.

The average mixed diet provides an abundant supply of minerals. There is little precise evidence to indicate that the arthritic has specialised requirements for any one of them. The general demineralisation of the skeleton of the atrophic arthritic and the local and occasional systemic trends in hypertrophic arthritics in the same direction may be regarded as emphasising a need for calcium and phosphorus. The anæmia of the chronic arthritic suggests an increased requirement for iron. While a reduced metabolic rate may arise from an iodine insufficiency there is little evidence to suggest such a pathogenesis for the reduced metabolic rate encountered among rheumatics.

The acid base residues of ordinary diets are suitable for arthritics who have reasonably satisfactory renal function. By this token special therapeutic claims for alkalising diets or supplements seem unwarranted. Certainly arthritics as a class do not present notable evidence of systemic acidosis. Hare (*loc. cit.*) and Gerson (*loc. cit.*) have attributed the favourable influences of certain vegetable dietaries to low sodium and high potassium contents. Both of these factors would tend to favour the reduction of extra-cellular tissue water, previously discussed. It may be noted that comparable influences upon extra-cellular fluid are involved in the use of external heat with sweating, purgation—both of which may be drastic and ephemeral in their results—massage, and the use of diuretics. As noted earlier, sub-maintenance levels of calories, or low-carbohydrate, high-fat rations, achieve the same result. Any regimen involving sub-maintenance must be entered upon with great caution. A sharply lowered caloric intake is usually more of academic than of clinical interest and one merit of the high-protein, high-fat, low-carbohydrate diet discussed is that it can be continued indefinitely, at any desired caloric level, without danger.

Water can be provided the arthritic *ad lib.*, consistent with renal function. The low-grade œdema shown by some rheumatics is best regulated by control of substances which " hold " water rather than by limitation of water intake. It may be observed in passing that water may be lost from body tissues even on a fluid diet. The Karrel diet of milk, for example, leads to a net water loss from the body, partly because of its caloric inadequacy and partly because of its high protein and low carbohydrate content.

The bulk—*i.e.*, the amount of indigestible residues—of dietary materials plays a rôle in gastro-intestinal motility. Arthritics presenting stasis are often benefited in this respect by foods with bulky residues. However, a considerable proportion of chronic rheumatic patients have digestive tracts abnormally irritable at some segment and are handicapped rather than benefited by this measure. While a few arthritics have a specific sensitivity to certain foodstuffs, this situation is comparatively rare and in any event must be handled as an individual problem.

Occasionally a dislike for certain classes of foodstuffs or an ill-advised restriction of foodstuffs may give rise to or contribute toward a nutritional deficiency. In addition to these habitual or artificial conditions, the chronically ill patient often develops a genuine anorexia. Under these circumstances tonics, supplementary amounts of vitamin B, or, rarely, insulin may be indicated as specific stimulants to appetite.

Summary

The sick arthritic presents a symptom-complex which must be regarded as a resultant of the cumulative effects of a " total war," by various factors, upon major aspects or systems of the body. Effective therapy requires a regimen of " total support " of the patient. There are obviously two therapeutic aspects to total support: one, in general, removes from the field such accessible factors as make for or constitute worry, fatigue, faulty body mechanics and focal infection; the other seeks to provide constructive factors such as rest, correction of anæmia, replacement therapy in the gastro-intestinal or endocrine system; tonic medication, sedation, physical therapy and optimal nutrition. Obviously these objectives and measures overlap.

Among the factors which, like rest, have widest application to arthritics as a group, is that of optimal nutrition, using that

term in a refined sense. Specific influences on the arthritic manifestations as well as generic influences may be achieved.

The arthritic presents atrophy of bone and muscle, anæmia, modified plasma protein and peripheral œdema. The correction of these disturbances requires by definition a diet which differs from that adequate for the individual in health. In addition to these systemic disturbances, the gastro-intestinal tract of arthritics as a group shows evidence of both anatomic imbalance and functional disturbance. Under such circumstances more than ordinary care is necessary in the provision of nutritive materials required for the maintenance, repair and reconstruction of tissue, whether damaged directly by faulty nutrition or indirectly as a result of the disease.

There are suggestive data indicating that certain symptoms encountered with significant frequency among arthritics may arise from partial vitamin deficiencies. Under such conditions, and indeed in most cases, the foodstuffs should be so balanced as to decrease rather than increase the demands for vitamins. Even in health the ration of vitamin to calories, not merely the amount of vitamins, must increase as the total calories increase. In view of the composition of the average dietary this usually requires that the carbohydrate be relatively reduced. Appropriate supplements of vitamins are also indicated.

The low-grade œdema characterising many or most arthritics is open to influence by rest and also by such drastic and ephemeral measures as sweating and purgation. Another and safe influence, however, is available through a dietary which makes away from rather than towards fluid retention. For this as well as for the afore-mentioned reasons, the dietary for the arthritic should be in general high in protein, reasonably high in fat, and somewhat restricted in concentrated carbohydrate foodstuffs.

Under ordinary circumstances, caloric requirements of the arthritic patient at rest in bed are met by the calculated basal output plus 10 per cent. Ample provision of biologically good protein (at least 1 gram per kilogram body weight) is indicated not only to meet immediate needs, but to replenish depleted atrophic tissues. The calories from carbohydrate should constitute from 35 per cent. to 50 per cent. of the total. The balance of the caloric quota is provided for by fats. Obvious exceptions to this generalisation are indicated for the grossly underweight or overweight patient, and for patients who have an

intolerance for fatty foods, though the principles involved in the above general distribution of the foodstuffs have application to nearly all cases. The arthritic requirements for other dietary factors—*viz.*, minerals, water, bulk and palatability—present no great departures from the usual.

When dietary supplies are adjusted to optimal levels, as above described, and in co-ordination with the demands of the arthritic, conditions are most favourable for convalescence. While recovery will occur in certain patients without taking these factors into account, in others it is of crucial or paramount importance. There are few, if any, arthritic cases in which the rate of recovery cannot be expedited by co-ordinating dietetic measures, as above described, with the many other agencies necessary in achieving " total support " of the patient.

Neglect of the physiological influences upon the arthritic syndrome, available through purposive dietary adjustments, has led to the development of cults in which under-nutrition or even starvation constitutes a routine therapeutic procedure. This uncritical application of certain nuclei of truth succeeds therapeutically in some cases robust enough to tolerate it and accounts for the success of such movements. It results in great injustice to asthenic arthritic subjects, however, and will probably continue to do so until the orthodox profession concerns itself more with the issues at stake.

FIBROSITIS

A Biographical Study of Fifty Civilian and Military Cases, from the Rheumatic Unit, St. Stephen's Hospital (London County Council), and a Military Hospital

By PHILIP ELLMAN, OSWALD A. SAVAGE, E. WITTKOWER, and T. F. RODGER

Fibrositis, a well recognised scourge of mankind, is certainly one of the commonest of the rheumatic diseases and is responsible for much social and economic disturbance. Davidson and Rae stated that in 1936 there were among the insured population of Scotland (35 to 40 per cent. of the total population) " no fewer than 50,000 cases " of rheumatism in its various forms which

caused the huge total of 3,500,000 days' incapacity, entailing an annual loss of two or three million pounds. Among an insured population of 500,000 persons in Ireland, according to O'Reilly, 16,000 claimed disability because of rheumatism during 1935. Rheumatism was responsible for the greatest number of claims, the largest amount of money paid out in claims (£131,000), and the greatest amount of incapacity (295,000 weeks in the year) of all disease in Ireland. In the United States, again, rheumatism is by far the most common chronic disease. Its incidence on a given day was estimated to be about 1 per 1,000 persons (United States Public Health Service, Bulletin No. 4).

The term fibrositis, since it was first introduced by Gowers in 1904, has become loosely applied and ill-defined. Patients complaining of vague pains shifting from one part of the body to another, where physical examination reveals little or nothing, are often labelled "fibrositis". Until recently American physicians have even doubted the existence of such a disease, but we believe that, within defined limits, it can be regarded as a clinical entity. This work is a study of a group of patients of this type who were attending the Rheumatic Unit at St. Stephen's Hospital, originally civilians but subsequently soldiers, particular attention being paid to the relative significance of physical and psychological factors in this disorder.

Much work has been done on the pathology of the condition (Stockman 1920, Slocumb 1936, Collins 1940), but an all-inclusive definition based on such work is lacking. Although the term fibrositis implies inflammation of fibrous tissue, neither inflammation alone nor the involvement of fibrous tissue alone can correctly define all aspects of the disease. There are, in fact, no pathognomonic pathological lesions found in this disease.

With regard to *ætiology*, as in the rheumatic diseases in general, such varied factors as occupation, climate, metabolic and endocrine disturbances, trauma both mental and physical, may each and all play their part. We agree with Clark Kennedy and Vaizy (1940) that oral sepsis in particular and focal infection in general are far too frequently regarded as the principal ætiological factors in rheumatism.

The psychogenic factor in chronic arthritis has received some attention: Jelliffe, White (1923), Nissen, Spencer (1936), Booth (1937), Ellman and Mitchell (1938), Cobb, Bauer, Whiting (1939); and its influence on the ætiology of fibrositis in the production

of psychogenic muscular pain as an outward manifestation of acute or chronic emotional disturbance, causing autonomic disturbances and vascular instability with ischæmia and muscle spasm has been discussed (Gordon 1930, Halliday 1937). Fibrositis, then, on clinical grounds, is an acute, subacute, or chronic condition, characterised by pain and stiffness, especially on movement. It occurs in the subcutaneous tissues, in fibrous origins, insertions and aponeuroses of muscles in fibrous portions of the capsule of joints, in fascial ligaments or tendons and supporting tissues of certain nerves. Some clinical abnormality should be present to support the diagnosis.

Industrial fibrositis is a common condition and probably results more frequently from multiple traumata (physical or mental) than from a single injury. Fibrositis of the back may not infrequently follow postural deformity with consequent strain on the muscles and ligaments. Chronic arthritis of the rheumatoid and osteo-arthritic types is not infrequently accompanied by fibrositis: in the former case the inflammation of the joints is accompanied by a periarticular fibrositis which is part of the major disease; in the latter, abnormal stress in the structure surrounding the affected joint is responsible. In a small number of cases we have observed an acutely inflamed focus of infection, such as, for example, the tonsils, para-nasal sinuses or gall-bladder, accompanied by an attack of fibrositis which subsides with the focus. This is in the nature of a transient bacteræmia, but damage is caused, a scar is formed and the original attack will recur.

Once a fibrositic area has developed, a number of conditions which would not in themselves have caused the original attack may be responsible for its recurrence—*e.g.*, fresh trauma, local change of temperature, an allergic incident with vascular spasm, an underlying gouty diathesis, some generalised toxæmia, or, as we have frequently observed, a period of mental stress.

Investigation into the *symptoms* of fibrositis shows that the pain is, for the most part, described as a dull ache comparable with toothache. It is frequently worst in the morning, associated with stiffness, improves as the part is loosened with movement, and recurs in the evening, often persisting through the night and causing insomnia. There are also sharp twinges of pain, brought on either by a particular movement or by pressure. Relief is difficult to obtain since it is only gained by supporting the limb and yet constantly changing the position of rest.

Clinical Examination.—There has been much dispute as to the importance to be attached to the finding of nodules (which may be painful or painless) in the diagnosis of fibrositis. These scars of past trauma or inflammation may be small round areas, large plaques, or thickened fibrous sheaths or septa. They may not be palpable because they are too deep or because they are covered by muscles in spasm. They can be felt in the origin, the insertion, or in the superficial or the deep ensheathing fibrous tissue. They can be felt in persons who have no attack of fibrositis, and conversely during an attack only a single plaque or nodule, or at most only a small proportion of them, will be painful. Clinical examination must determine which area of soft tissue is inflamed and responsible for the pain, for, as Kellgren has pointed out, the pain of superficial trauma is felt immediately over the area, whereas that due to deeper trauma is referred some distance away.

The question as to whether a particular area of thickening is responsible for the symptoms can be answered by two simple tests. If palpation reproduces the pain of which the patient complains, and if for a time after infiltration of that area with a local anæsthetic palpation is negative, then it is safe to assume that the thickening is the seat of the fibrositic lesion. The other test is performed by increasing tension in the suspected structure, in a muscle by contraction, or in a ligament, tendon, or band of fascia by stretching. Such a manœuvre will reproduce the pain if the structure contains the fibrositic area.

Muscle wasting is slow in making its appearance in fibrositis, but will occur after repeated attacks in the same area when loss of power also ensues. Apart from the symptoms here described "fibrositic" patients are usually healthy and the search for a focus of infection frequently proves abortive.

Material and Method of Examination

Biographical studies were made of 50 patients labelled fibrositis, aged nineteen to sixty-one on examination and seven to sixty-one at onset. Their average age was thirty-seven years on examination and twenty-seven years at onset. The duration of illness varied from three months to forty years: in 14 cases it was of less than one year's standing, in 17 of over ten years' standing. Fifteen were women, 35 men: of the latter 32 were soldiers. In 38 of the patients, including soldiers, the civilian

occupations were classed as manual work. Many of them were in occupations generally regarded as predisposing to " rheumatism "—miners, quarrymen, bricklayers, stokers, coalmen, cooks and laundry workers. Twenty-three of the patients were seen by us at the Rheumatic Unit, St. Stephen's Hospital, London; the remainder were referred to us without selection from various military and emergency hospitals.

FINDINGS

Symptoms

1. *Pain.*—Of the total of 50 patients, pain confined to a group of muscles—as in lumbago or sciatica—was complained of by 26; this was accompanied by pain in various parts of the body in 14, and by pain which " travelled " or " shifted " from one part of the body to another in 6. Four patients complained of pain " all over the body." A fair number of patients complained of tingling, tickling, heaviness or tightness in the affected parts, others of an ache, but the vast majority described their pain as " burning," " gnawing," " piercing," " tearing," " twisting," " shooting," or, more emotionally, as " nagging," " depressing," " excruciating " or " agonising." The pain was intermittent in about two-thirds and continuous in about one-third of the patients. It was aggravated in almost all of them by exertion, cold and exposure.

2. *Stiffness.*—Minor degrees of stiffness were present in practically all of the patients; definite limitation of movement was complained of by about half of them. Three patients were of the " bent-back " type (camptocormia)—*i.e.*, having once bent down they are almost unable to straighten themselves.

3. *Weakness.*—Weakness in the affected part resulting in limitation of movement often combined with general lassitude and easy fatiguability was prominent in 21 patients. Not uncommonly they stated that one of their limbs was " paralysed " or they displayed disabilities varying from limping to bizarre gait disturbances.

Patients' Clinical Experience

The prevailing diagnosis in these patients was rheumatism or fibrositis; others had been diagnosed as neuritis or sciatica. Many of them, on their long pilgrimage from doctor to doctor,

had acquired many labels and had been subjected to many modes of treatment appropriate to the labels which suggested that the complaints described by them had baffled or misled their doctors.

Here is a typical example.

A female patient, aged fifty-three, had suffered from pains in various parts of the body almost continuously from the age of thirteen, when she was said to have been treated for " chronic inflammation of the kidneys." Subsequently the pain shifted to the heart region and, according to the patient, various doctors stated that her heart was " awfully dilated back and front." After that, at about twenty-five, she had " queer attacks of pain " in her stomach and " the doctor said I wouldn't survive another attack." At twenty-eight her appendix was removed and was found to be " abnormally long." The backache was thereafter attributed to a " very bad displacement of the uterus " and " a big specialist " performed a hysterectomy and oöphorectomy. After that the pain was worse than ever. Pain in her left arm prompted a surgeon to put the arm into plaster and, this having failed, all her teeth were removed. When eventually she attended the Order of St. John Clinic in London, she stated that she had " laryngitis, bronchitis and the heart was very tired and had a bit of myocarditis too." She also had " starting arthritis in the wrists, ankles and knees and fibrositis in the neck and shoulder." No organic changes were found.

Physical Examination

This consisted of a thorough clinical overhaul with particular relation to the painful area, and local X-ray of certain joints.

In a portion of the series (20 cases at St. Stephen's Hospital), the blood-count, sedimentation rate, Wassermann reaction, gonococcal fixation test, and blood uric acid estimation were invariably done.

Group I.—Twenty-three cases. In these patients the physical examination was negative. Points of tenderness, when present, were not constant in position on successive examinations. The pain could not be reproduced by palpation of these localised areas and could not be abolished by infiltration with 2 per cent. procaine.

In some there was generalised hyperæsthesia over a wide area but no local change in the skin, no changes of sensation to light touch, pin-prick, or heat and cold. Complaints of weakness or

loss of power were not substantiated by physical examination and no evidence of muscle wasting was found.

Many of these patients put forward "creaking" joints as evidence of the presence of rheumatism, but no crepitus was felt or heard on movement of the joints and X-ray showed no irregularity of the joint surfaces and excluded the possibility of loose bodies which might have caused the symptoms.

In patients who complained of limitation full movement was obtained on examination.

Group II.—Twenty-seven cases. In these some physical abnormality was found on examination.

(*a*) Eight cases. Tender localised areas or nodules where pressure reproduced the specific pain. This could be abolished temporarily by infiltration around the tender points with 2 per cent. procaine.

(*b*) Eight cases. In these an evident focus of infection was found and the history strongly suggested a relationship between the activity of the focus and the activity of the fibrositis.

(*c*) Four cases. Postural deformities of the spine, scoliosis, lordosis or kyphosis, accompanied by tenderness along the spinal muscles.

(*d*) Four cases. Sacro-iliac strain. In these cases there was a history of sudden onset related to trauma and on examination there was found a raising of the pelvis on the painful side with tenderness over the affected joint. The pain could be reproduced by rotation of the pelvis upon the spine.

(*e*) Two cases. Radiological irregularity of the joint surfaces was accompanied by tenderness, wasting and spasm on movement of the surrounding muscles.

Osteoarthritis is, of course, inevitably accompanied by a localised fibrositis.

(*f*) One case of congenital bony deformity with fibrositis of the surrounding tissues.

Psychiatric Examination

The 25 patients who showed evidence of hysterical features were classified as hysterical.

The prevailing psychological symptom in the history of 7 patients was anxiety, and they were labelled for descriptive purposes as anxiety states; 3 suffered from depressive states and 3 could only be termed psychopathic personalities (two of

them of the shiftless and one of the over-aggressive type). Character deviations which were apparently unrelated to the rheumatic complaint existed in 5 patients; 2 of them were pathologically over-conscientious and 3 abnormally shut-in. No psychological anomalies were found in 7 patients.

Hysterical.—It must be pointed out that the term "hysterical" is deliberately used in a very broad sense and includes hysterical reactions. It is meant to cover the following types:

1. *Histrionic Type.*—Seven female patients displayed remarkable emotional instability on examination. They oscillated rapidly between moods of unwarranted hilarity, anger and despair; they laughed uproariously one minute, attacked the interviewer venomously the next, and shortly afterwards were in a flood of tears. In 5 of them the history of "rheumatic" complaints was of very long standing (over thirty years' duration in 3 cases). The tenacity of their complaints had misled previous examiners and had prompted them to perform apparently useless surgical operations. These patients were theatrical in the description of their complaints and in the account of their long and eventful life histories. A few of them reported "paralysis" of limbs which had yielded to miraculous cures, or described visceral symptoms which in the opinion of previous doctors had been due to "nerves."

2. *Plaintive, Ailing Type.*—Two were of this type; one of them, a soldier, had been prevented from doing any work since the last war by "chronic malaria", the existence of which had never been confirmed.

3. *Resentful Type.*—In 15 patients "fibrositic" complaints started or existed under life conditions which were likely to provoke resentment. The circumstances of their lives at the time of onset or shortly afterwards strongly suggested the possibility of a purposive utilisation of their incapacitating symptoms as a defence against difficulties (*i.e.*, suggested the possibility of a hysterical origin or at least of a hysterical exploitation of their symptoms). This applies to a number of soldiers who had been spoilt and pampered in their early days and who resented the hardships imposed by Army life; it also refers to men of over-dependent type who suffered badly through separation from their families, and lastly to men of good education who were forced to serve as privates. A female Austrian refugee patient who had been brought up in well-to-do circumstances started

suffering from unbearable pain in her arms when compelled to work as a housemaid in this country, and a soldier who loathed being in the Army made a splendid recovery from his previous intractable " rheumatic " complaints shortly after his discharge from the Army.

4. *Malingering.*—Malingering was suspected in a soldier, a " good-for-nothing " in civilian life, who was anxious to get out of the Army by hook or by crook. At times it is difficult to draw a line between malingering and a need or desire unrecognised by the patient to evade painful circumstances.

Here are some typical examples:

I. Hysterical Group.

1. *Histrionic Type.*—A tailoress, aged fifty-five, stated that she had acute rheumatism all over her body when she was twenty-one. The rheumatism affected her heart and she almost died. " They tried to get the rheumatism away from my heart and it went to my head. I didn't seem to be myself." Following on this she could not walk for a year. At thirty-one she lost the use of her left arm for three months; at forty her limbs were paralysed and she had " heart attacks "—acute pain underneath the left breast and shortness of breath. Examination at a heart hospital was negative. A year afterwards she had a bad attack of lumbago. When she stooped she could not straighten herself. For the last two years she has suffered from pain across the shoulders, in the back, in both knees and in the right thumb.

Physical examination: Obese, generalised tenderness, full movement of both shoulders. Thumbs swollen at metacarpo-phalangeal joints. B.S.R. $\frac{3}{200}$ (Westergren, 1 hr.); X-ray: Osteo-arthritis of thumbs; shoulders and neck nil. Blood uric acid 2·4 mgm. per cent.

Diagnosis: Fibrositis of shoulders. Osteoarthritis of thumb joints.

Psychiatric examination: One of two sisters, the patient is the daughter of an ill-tempered father, who is a periodical drinker, and of a hysterical mother unfaithful to her husband. Her mother died when the patient was seventeen years of age. Despite these very unfortunate home circumstances the patient was a jolly child, impulsive, stubborn, mischievous, and only happy when she was in the forefront. At twelve, when she had to pass an examination, she was rather nervous beforehand and ever since

has suffered from trembling fits. At puberty the patient went through a very tearful phase. At nineteen she had an unhappy love affair, which came to an end at twenty-one (onset of rheumatic fever). While she was in hospital with rheumatic fever her father remarried. The patient resented his marriage and intensely disliked her stepmother, who was very rude to her. The patient then had a relapse of rheumatic fever which, as she stated, affected her heart and her mind. She lay in bed, constantly shouting for her deceased mother. After a further admission to hospital she made an unsuccessful attempt to strangle herself. "I used to sing at times and fancy I was a child again." Her complete recovery was eventually effected by the kindness of a nurse who resembled her mother in appearance. The patient's married life was a failure. Her husband was a heavy drinker, and was unfaithful to her with her own sister, who had a child by him. Owing to her husband's drinking habits, they got into severe financial difficulties and consequent worry made her ill again ("heart" attacks, paralysis of limbs). A year afterwards, after a prolonged illness during which the patient nursed him self-sacrificingly day and night, her husband died. Subsequently the patient had to work very hard to keep herself and the adopted son of her sister. At the outbreak of war she lost her job (relapse of her rheumatic complaints).

On examination the patient trembled almost continually; she was very emotional, sometimes laughing without justification and sometimes bursting into tears.

2. *Plaintive, Ailing Type.*—A soldier, aged twenty-eight, four or five years ago began to suffer from pain in both thighs, travelling round the knees. The pain did not interfere a great deal with his work in civil life, but it has become worse since he joined the Army. He feels unfit for P.T. and during cross-country runs his legs feel stiff and he lags behind. He has reported sick repeatedly. At times he has been excused all duties; at other times he has been on light duty. Treatment has been without avail.

Physical examination : Negative.

Diagnosis : Fibrositis.

Psychiatric examination : This is a man of small stature who, from early childhood onwards, has been constantly ailing. Being delicate in health he was spoilt and pampered by his mother, to whom he was greatly attached. He was unfit for games and

preferred playing quietly indoors to the rough and tumble outdoors. He was a quiet and reserved boy, devoid of aggressiveness, painstaking in the performance of his duties, and apt to worry unduly. Owing to ill-health he was off school a great deal. After leaving school he worked as a stencil printer. As long as his work was not too strenuous he got on well. Since early childhood, painfully aware of his poor physique, he has been of a non-assertive type and liable to give up before he has properly started. " When other boys jumped ten feet I was satisfied with jumping five," he said. Whatever demands were made on him he always felt he could not " stand up to it." After conscription he tried hard to keep up with his comrades, but he soon realised that he could not do so.

3. *Resentful Type.*—An airman, aged thirty, has complained of pains in the wrists, in the right shoulder blade, knees and ankles since his transfer to Scotland some months ago. He notices that his joints creak. He also suffers from headache and has gone off his food.

Physical examination : Joints tender on extreme flexion; no other findings.

Diagnosis : Fibrositis.

Psychiatric examination : From early childhood onwards this man has been grossly over-attached to his over-lenient, over-anxious and over-protective mother; when he talked about her, tears came into his eyes. Early in life, obviously as a defence against the over-dependence on his mother of which he was vaguely aware, he adopted an attitude of defiant independence. Although, underneath, he was shy, timid, self-conscious and over-sensitive, he put on an air of self-assurance, aggressiveness and bravado. Because of the feeling of inferiority, which must be the result of basic timidity and dependence, he always wanted to do things better than anyone else. After leaving school he worked his way up from an errand boy to a traveller for a draper's firm. In 1936 he joined the Special Police and " two years, three months and four days ago " he married. He chose his wife because she resembled his mother in many respects. His married life has been very happy indeed; his wife mothered him a great deal. Just before Christmas, 1939, his wife gave birth to a child which died shortly afterwards. When he spoke about this incident he cried again. In June, 1939, knowing that he would have to join up, he volunteered for the R.A.F. in the hope of being kept near

his family. "They promised to post me as near home as possible." After joining up, however, he was first sent to another part of England and afterwards to Scotland. He worries a great deal about the welfare of his family and feels very resentful about being posted far away from them. "If I could get down there, I wouldn't mind sitting on top of a balloon with a machine-gun, just to be beside them," he said.

Soon after his arrival in Scotland he fell ill and applied for a transfer to the south as he thought that the climate in Scotland did not agree with him.

II. Anxiety States.

A soldier, aged forty, in 1932 started suffering from pains in the right shoulder, the right side of the chest and the right side of the neck. These pains returned every year with varying intensity. They usually became worse in autumn and better in spring. He joined up as a volunteer in August, 1940, and started having a particularly bad turn of rheumatism in November.

Physical examination : Negative.

Diagnosis : Fibrositis.

Psychiatric examination : One of 16 children, this man grew up in great poverty, in dire need of food and clothes. With the family lived his psychotic grandmother, who suffered from nightmares and often wandered aimlessly in the streets. His mother, having so many children, had very little time for him, and though he was fairly well cared for he badly missed and wanted parental affection. He described himself as an unusually shy, oversensitive and timid child, anxious to conceal these characteristics in front of others. He was absolutely terrified of darkness and, having the example of his grandmother before him, was haunted by a fear of insanity. On one occasion, in the dark, he jumped from the top to the bottom of the staircase with fright. Like his grandmother, he suffered from nightmares and also from fainting bouts and bed-wetting. At seven he was night-blind for some time. After leaving school he worked in the pits. From the start he was afraid of being killed by falling stones or being buried alive. Though completely scared he "stuck it" for some considerable time until, when he was twenty-four, two of his friends were killed. One of them was dragged to death by a pony, the other had his neck pulled out. After this he broke down and was unfit for work for three years. "When I had the

nervous breakdown I was nervous of everything. I was frightened of my own shadow." He developed a feeling of incompetence and inferiority which made him retire completely from social contacts. As he felt that other people were staring at him, he did not even dare to take a tram. He also suffered from peculiar twilight states. Lying in bed he would see someone standing by his bedside, and, unable to speak, he started to scream. At twenty-seven, unwillingly, he returned to pit work, and at thirty-two his present rheumatic symptoms started. His nervous symptoms, although they have improved, have persisted until now. Shortly after his enlistment his rheumatic complaints became worse.

III. Depressive States.

A corporal, aged forty-one, has suffered from "rheumatism" for thirteen years. As time went on he saw various doctors, but treatment was without avail. In 1938 he joined the Army as a cook. Though he did not feel too well he just carried on, until he felt he could not carry on any longer. He complains of pain in both hip joints, in the stomach and in the "heart muscle." When he wakes up in the morning he feels as if he were a hundred and not forty-one.

Physical examination: Negative.

Diagnosis: Fibrositis.

Psychiatric examination: At the age of two this man was "nearly dead" with diphtheria. At six he met with a serious accident. While he was playing with some children a big stone fell on his back. "It nearly broke his spine." For nine months afterwards he was on crutches, and ever since he has felt a weakness in his back. Dating from this accident he was a shy, retiring boy who preferred to roam alone in the country brooding over metaphysical problems, to the company of other children. On his long lonely walks, death and dying was a main subject of his rumination. Life never seemed to him "full of joy and sunshine." "I used to think when I was ten years old that I had lived a terribly long time and that I might not live much longer." If forced into company he was shy and felt very unhappy. "I felt I was a different person, out of the picture, altogether not one of them." He has always imagined that people are watching him. He was a timorous little boy, frightened of policemen and scared of graveyards. Until eleven

he was a bed-wetter and until fifteen a stutterer. At nine he left school, went to a training ship and worked himself up to a Master of Arms. At sixteen he married and subsequently became a qualified quarryman. He described himself as a man with a severe sense of duty. "Work first and pleasure afterwards" has always been his motto. He still shuns company and spends the little spare time he allows himself on writing poetry. He is still subject to spells of depression for no definite reason. He worries a great deal about his present illness, which he believes will be fatal. He would like to see his children grow up before something happens to him.

Other Ætiological Factors.

1. "*Rheumatism*" *in the family:* Thirty of the 50 patients stated that there were other cases of rheumatism in the family.

2. *Accidents:* An accident preceded the onset of the complaint in 6 patients. Of these, 3 had no evidence of a structural lesion, 1 of them being an anxiety neurotic, the 2 others hysterics. The remaining 3 patients showed no relevant psychiatric anomalies and their complaint was sufficiently explained by the physical findings. Ten patients had serious accidents as children, which might have created a *locus minoris resistentiæ*.

3. *Infection:* Prior to their rheumatic complaint, 11 patients suffered from an acute febrile illness which was described as "rheumatic fever" by 3, acute tonsillitis by 2, cystitis by 2, and a chill, pleurisy, carbuncle, malaria, each by 1. A retrospective assessment of the validity of these statements is impossible; in the absence of this it may be assumed that the fibrositic complaint was of infectious origin in some and in others was undoubtedly prolonged and exploited on a hysterical basis. Three patients with definite evidence of focal infection were without gross psychiatric abnormalities and belonged to the group of those with major physical changes.

4. *Exposure:* Half of the patients (26) were, prior to or at the time of the onset of their complaint, in occupations which are generally regarded as favouring the development of rheumatism—*e.g.*, miners, coalmen, bricklayers, quarrymen, drivers, cooks. Of 9 patients who explicitly attributed their complaint to exposure to dampness or inclement weather, 5 were soldiers of the resentful, hysterical type, with no or insignificant physical changes; 2 others were depressive.

TABLE I.

	Total.	*Localised Pain.*	*Shifting Pain.*	*Pain in Different Parts of the body.*	*Pain "all over the body."*	*Ratio of localised Pain/Vague Pain.*
Significant psychological disorder.	35	13	6	12	4	13/22
No significant psychological disorder.	15	13	0	2	0	13/2

TABLE II.

	Total.	*No Significant Physical Findings.*		*Significant Physical Findings.*		*Ratio of no Significant Physical Findings to Significant Physical Findings.*
		No Physical Findings.	*Merely tenderness on Pressure or Pain on Movement.*	*Minor Objective Findings.*	*Major Objective Findings.*	
Significant psychological disorder.	35	11	9	14	1	20/15
No significant psychological disorder ..	15	0	3	7	5	3/12
Ratio of significant psychological disorder to no significant psychological disorder.		20/3		15/12		

CORRELATION OF PHYSICAL AND PSYCHIATRIC FINDINGS

1. *Nature of Pain in relation to Psychiatric Diagnosis.*—If, for the sake of comparison, the patients are divided into group 1, those in which there is reason to believe that the complaint has arisen on a basis of a psychological disorder (hysterical group,

anxiety states, depressive states), and group 2, those in which such evidence does not exist, it has been shown (Table I) that, out of 35 patients of the first group, 13 suffered from localised, 6 from shifting pain, 12 from pains in different parts of the body, and 4 from " pains all over." On the other hand, of 15 patients of the second group, 13 had localised pain and only 2 had pains in separate parts of the body. The comparison of the two groups, therefore, demonstrates what might have been expected, that a complaint of vague shifting pains is suggestive of an underlying emotional disorder, while a complaint of strictly localised pain points to the presence of organic changes.

2. *Physical Findings in relation to Psychiatric Diagnosis.*—Twenty out of 35 patients with significant psychological disorders (*i.e.*, about two-thirds), in contrast to 3 out of 15 patients with no significant psychological disorders (*i.e.*, one-fifth), had no traceable objective changes likely to be the basis of their complaint (Table II). With only one exception, all patients with major physical changes are to be found among those with no significant psychiatric anomalies. Minor objective findings are fairly common in those suffering from significant psychological disorders (in 14 out of 35); they probably determine the localisation of symptoms in psychologically predisposed individuals. The infrequency of severe psychological disorders in patients with gross organic changes disposes of the argument that the psychiatric abnormalities encountered might be secondary in nature and due to the prolonged incapacitating illness. Detailed analysis of the correlation between specified psychiatric diagnoses and findings on physical examination gives no clear-cut results, owing to the small size of the groups; however, as one might expect, most of the patients in whom physical examination provoked unbearable pain without any traceable lesion are to be found in the hysterical group.

Review of Literature

The data obtained tally, at least in principle, with those found by other writers.

Halliday, surveying a series of 145 consecutive patients labelled " rheumatism " (including fibrositis, lumbago, sciatica and neuritis), found that 57 of them (*i.e.*, 39 per cent.) were incapacitated because of psychoneurosis. Thirty-seven per cent. of a further similar series of 62 patients examined by

the same author were regarded as being disabled because of psychoneurotic disturbance. The incidence of "psychoneurotic rheumatism," according to this author, rises still further—to 40 to 60 per cent.—if only those patients are considered who have been for two months or more on the sick list.

Sir Arthur Hurst from his extensive experience in the last war states: "A patient with genuine sciatica almost always recovered within two or three weeks if he was given complete rest. If the pain persisted after that time, it was almost always a result of hysterical perpetuation of what had originally been organic. This was true even if the ankle-jerk on the affected side was diminished or lost; but accurately localised tenderness along the nerve associated with pain produced by each of the various methods of stretching the nerve (Lasègue's, Bonnet's and Néri's sign) made one hesitate to diagnose a functional condition. Though one of these signs might be present, all were very rarely found in soldiers after the first fortnight and, corresponding with this, all or nearly all soldiers who did not give all the signs were cured by simple psychotherapy. Though malingering was very rare in the war, I think that sciatica and lumbago were the two conditions which were commonly exaggerated or even simulated more often than any other. The duration of a genuine attack of lumbar fibrositis was even shorter than sciatica. It was found at Bath in the last war that rheumatism in soldiers did not respond to spa treatment as well as it did in civilians. This was because it was largely hysterical. The 'bent back of soldiers' which was often a sequel of fibrositis was always hysterical."

The neurotic implications of backache have been discussed in some detail by Jones, Lovett, Whitman, Wechsler, Goldscheider, Brun, Levy, Geronne, McGregor and Fetterman. Most of these authors, like Hurst, describe certain types of backache and limitation of spine movement as hysterical manifestations.

Fibrositis-like complaints, however, are not only confined to hysterics; Gordon and Halliday agree that they are also commonly found in anxiety neurotics and depressives. Their frequent occurrence in individuals of obsessional make-up, noted by some writers, could not be confirmed by our observations.

Discussion and Conclusions

Investigation of 50 patients labelled as fibrositis showed that 35 suffered from common psychological disorders bearing on and of probable ætiological significance for their complaint. Twenty-five of the 35 were classed as hysterical conditions, 7 as anxiety states, and 3 as depressive states. Only long-standing cases were included in the series; this selection (see Hurst above) probably accounts to some extent for the high percentage of psychoneurotics among the patients studied. Despite typical complaints, no clinical evidence of the presence of fibrositic muscular changes could be obtained in a certain number of cases; in others, where these were present, emotional factors seemed to exaggerate or perpetuate the complaint, which may originally have started on an inflammatory or ischæmic basis. It is possible that "fibrositic" changes are the physiological accompaniments of emotional tension and psychological conflicts of a relatively specific nature. The possibility of secondary psychological changes due to the prolonged nature of the physical disorder can be safely excluded in the majority of cases, since psychological abnormalities were absent even in cases of very long standing where the complaint was sufficiently explained by the presence of gross structural lesions.

The presence of a very large number of hysterics in the series suggests that in these the main symptoms of the disorder—pain and limitation of movement—originate in an anxiety-driven craving for sympathy and represent an appeal for it. Without recognising this situation by their symptoms, patients of histrionic type draw attention to themselves, while those of the resentful type show the world how harshly they have been treated, and those of the plaintive type demonstrate their need for care. At the same time all of them aim at and actually achieve an escape from painful circumstances into the childish sheltered existence of the sufferer. In the anxiety neurotic and in the depressive, the martyrdom of pain gratifies his self-punishing tendencies which have arisen from guilt over deep-seated instinctive drives.

Beyond this, observations on individual patients and considerations of a more general nature point towards conflicts over aggressiveness in the patients concerned. The resentful, plaintive and histrionic attitude of the group of patients classed as hysterical contains aggressive elements, and anxiety and

depression are known to be due to repressed self-directed aggression. The muscles serve as means of defence and attack in the struggle for existence, and internal tension is most easily released by muscular action. Hence, if the external expression of aggressiveness in the form of muscular action is inhibited by repressing forces operative in the individual, muscular tension may result which is felt by the individual as pain and limitation of movement, and is erroneously interpreted by the examining doctor as fibrositis.

Similar views on the psychodynamics of muscle tension have been expressed by Reich, Wolfe and Dunbar, and by Halliday in dealing with psychoneurotic rheumatism.

Summary

1. Thirty-two military and 18 civilian patients diagnosed as fibrositis were submitted to a routine clinical and a special psychological examination. Only cases of more than three months' standing were included in the series.

2. In 23 patients of the total of 50, the physical examination was negative; in 27 some physical abnormality was found: tender localised areas or nodules where pressure reproduced the specific pain and procaine infiltration abolished it; cases with strong evidence of focal infection, with postural deformities of the spine, with a history of sacroiliac strain, with radiological irregularity of joint surfaces accompanied by tenderness, wasting and spasm on movement of the surrounding muscles.

3. Twenty-five of the 50 patients showed hysterical features, 7 suffered from anxiety states and 3 from depressive states. Those with hysterical features were subdivided into histrionic, plaintive and resentful types. One patient only seemed to be a malingerer.

4. Ætiological factors other than psychological were discussed.

5. A complaint of vague shifting pains is suggestive of an underlying emotional disorder, while a complaint of strictly localised pain points to the presence of organic change. Correlation of physical and psychiatric findings shows that the severity of psychological disorders is in inverse proportion to the severity of organic changes—*i.e.*, the majority of patients with significant psychological disorders had no, or minor, organic changes, whereas very few of those with gross organic changes had significant psychological abnormalities.

6. The findings obtained tally, in principle, with those of other writers.

7. The psychodynamics of complaints mimicking true fibrositis were discussed.

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